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Molybdenum cofactor deficiency

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<td>molybdenum cofactor, MoCo, MOCS1, MOCS2, MOCS3, GEPH</td>
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Molybdenum cofactor deficiency: Mutations in GPHN, MOCS1 and MOCS2

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ABSTRACT

All molybdenum-containing enzymes other than the bacterial nitrogenase share an identical molybdenum cofactor (MoCo), which is synthesized via a conserved pathway in all organisms and therefore also is called “universal molybdenum cofactor”. In humans, four molybdoenzymes are known: aldehyde oxidase, mitochondrial amidoxime reducing component (mARC), xanthine oxidoreductase and sulfite oxidase. Mutations in the genes encoding the biosynthetic MoCo pathway enzymes abrogate the activities of all molybdoenzymes and result in the “combined” form of MoCo deficiency, which is clinically very similar to isolated sulfite oxidase deficiency, caused by mutations in the gene for the corresponding apoenzyme. Both deficiencies are inherited as an autosomal-recessive disease and result in progressive neurological damage and early childhood death in most cases. The majority of mutations leading to MoCo deficiency have been identified in the genes *MOCS1* (type A deficiency), *MOCS2* (type B deficiency), with one reported in *GPHN*. For type A deficiency an effective substitution therapy has been described recently.

KEYWORDS: molybdenum cofactor, MoCo, *MOCS1, MOCS2, MOCS3, GPHN*
Historical Background

The existence of a molybdenum-containing cofactor had been first postulated in 1964 (Pateman, et al., 1964) after the discovery of a series of pleiotropic mutations in the fungus *Aspergillus nidulans*, all of them affecting the enzymes nitrate reductase and xanthine dehydrogenase (hence the gene symbol *cnx* for cofactor of nitrate reductase and xanthine dehydrogenase, Table 1). The biosynthetic pathway leading to the cofactor and shared among all free-living organisms (Fig. 1) was elucidated mainly in the bacterium *Escherichia coli*, where its absence leads to chlorate resistance under anaerobic conditions (Rajagopalan and Johnson, 1992). This resulted in the gene symbol *chl*, which later in an attempt to unify the different nomenclature (Shanmugam, et al., 1992) was changed to *moa* through *mog* (see also Table 1).

The first case of a MoCo deficiency (MIM# 252150) has been described no earlier than in 1978 (Duran, et al., 1978) and the precise nature of the disease was only recognized in 1980 (Johnson, et al., 1980). The observation of two complementation groups among fibroblasts from different MoCo-deficient patients (Johnson, et al., 1989) was the basis to the understanding of the molecular basis of the human disease, which finally resulted in the identification of the gene *MOCS1* (Reiss, et al., 1998a; Reiss, et al., 1998b) mutated in the type A deficiency (MIM# 603707), and the gene *MOCS2* (Stallmeyer, et al., 1999a) and its mutations (Reiss, et al., 1999b) resulting in MoCo deficiency type B (MIM# 603708). Subsequently a mutation in the *GEPH* gene, resulting in the only described case of a type C deficiency (MIM# 603930), was reported (Reiss, et al., 2001).
Molybdenum deficiency versus MoCo deficiency

Anecdotic reports on molybdenum toxicity in humans might originate from the well-documented adverse effects of elevated molybdenum levels on ruminants. This effect, however, is strictly limited to the special conditions in the rumen (Clarke and Laurie, 1980). In fact, the human body can adapt to a wide range of molybdenum uptake (Novotny and Turnlund, 2007). Due to the ubiquitous presence of molybdenum in organic food a dietary-induced deficiency of molybdenum cannot be induced in animal models (Rajagopalan, 1988). Accordingly, only one case of molybdenum deficiency has so far been described worldwide, which has been observed after prolonged total parenteral nutrition of a Crohn’s disease patient under omission of molybdenum supplementation (Abumrad, 1984). The possibility of a beneficial effect of drastically elevated levels of molybdenum on type C MoCo deficiency patients will be discussed below.

In contrast to molybdenum or molybdate, respectively, MoCo or its precursors cannot be recycled from nutritional sources. The simultaneous absence of endogenous rescue pathways requires all MoCo molecules to be synthesized de novo. All proteins involved in MoCo biosynthesis are encoded by autosomal genes and heterozygous mutations do not result in a noticeable phenotype. Homozygosity for non-functional mutant forms of any of the involved proteins, however, abolishes MoCo biosynthesis completely and thereby the activity of the MoCo-dependent enzymes sulfite oxidase, xanthine oxidoreductase, mARC (Havemeyer, et al., 2006) and aldehyde oxidase.
Phenotype and diagnosis

Four MoCo-dependent enzymes are known in humans: aldehyde oxidase, mARC, xanthine oxidoreductase and sulfite oxidase. No isolated form of aldehyde oxidase or mARC deficiency are known, which might originate from overlapping substrate specificities of the enzymes. Classical xanthinuria type I is the result of an isolated xanthine oxidoreductase deficiency (Ichida, et al., 1997), while classical xanthinuria type II is caused by a defect in the molybdenum cofactor sulfuration by HMCS (Fig. 1) prior to incorporation into xanthine oxidoreductase and aldehyde oxidase (Ichida, et al., 2001). In symptomatic patients xanthine stones due to elevated levels of xanthine are the most prominent effects, although they are not life-threatening. Isolated sulfite oxidase deficiency (MIM# 606887) is also an autosomal-recessive genetic disease even rarer than the “combined” MoCo deficiency. 21 cases worldwide have been summarized previously (Tan, et al., 2005).

Isolated sulfite oxidase deficiency and the combined deficiency of all MoCo-dependent enzymes due to MoCo deficiency are clinically indistinguishable and can be differentiated only by biochemical parameters like elevated xanthine and lowered uric acid as a result of the simultaneous loss of xanthine oxidoreductase deficiency in the combined form. They should be considered in the differential diagnosis of hypoxic-ischemic encephalopathy (Topcu, et al., 2001) and neonatal hyperekplexia (Macaya, et al., 2005). Both forms can simultaneously be detected by the use of commercial strip tests originally developed to measure sulfite concentrations in
wine and other beverages. False-negative results, however, are frequent, when the test is used shortly after birth (when the sulfite has not accumulated sufficiently for a positive test (Carragher, et al., 1999)) or when urine samples are not tested immediately and the sulfite is oxidized non-enzymatically. Sulfur-containing drugs can cause false-positive results. Metabolic changes are summarized in Fig. 2.

Elevated sulfite levels lead to progressive neurological damage (Sass, et al., 2003; Zhang, et al., 2004), while the contribution of other metabolites such as taurine, S-sulfocystein and thiosulfate to the disease progression is not yet fully understood (Abbas, et al., 2008). Usually seizures start shortly after birth and feeding difficulties remind of amino acid intolerance. Those patients who survive the neonatal period in most cases show severe mental retardation as well as dislocated lenses and usually do not learn to sit or speak. The first 15 patients have been summarized elsewhere (Johnson and Wadman, 1989). Further reports followed (Appignani, et al., 1996; Arnold, et al., 1993; Coskun, et al., 1998; Hahnewald, et al., 2006; Ichida, et al., 2006; Ichida, et al., 2001; Kavukcu, et al., 2000; Leimkuhler, et al., 2005; Macaya, et al., 2005; Parini, et al., 1997; Per, et al., 2007; Pintos-Morell, et al., 1995; Salman, et al., 2002; Salvan, et al., 1999; Sass, et al., 2010; Schuierer, et al., 1995; Serrano, et al., 2007; Slot, et al., 1993; Teksam, et al., 2005; van Gennip, et al., 1994).

In general, the disease is not apparent at birth. Within the first week, feeding difficulties are observed accompanied by tonic/clonic seizures refractory to anticonvulsants with a prominent opisthotonus and an exaggerated startle reaction. A cerebral atrophy results in microgyria,
bilateral ventricular enlargement and is probably also responsible for facial dysmorphic features. A few patients with relatively mild symptoms have been described with presumably at least one mutation allowing for significant residual enzyme activity. Although uric acid levels here occasionally were found to be normal (Arenas, et al., 2009; Johnson, et al., 2001), the biochemical parameters apparently do not correlate with the severity of the disease (Hughes, et al., 1998; Mize, et al., 1995; Ngu, et al., 2009).

It had been suggested that the observed brain anomalies could at least in part be also attributable to a sulfate deficiency rather than sulfite toxicity (Rajagopalan and Johnson, 1992), but neuropathological investigation (Salman, et al., 2002) and studies in animal models (Reiss, et al., 2005) did not support this hypothesis. The disease has been found in a variety of ethnic groups and all over the world, although it might be under-recognised in many countries. De novo mutations so far have not been described, but recently the first case of an uniparental disomy responsible for MoCo deficiency has been reported (Gumus, et al., 2010). Obligate heterozygotes display no symptoms. Prenatal diagnosis by enzyme activity assays has been described using amniotic cells and chorionic villi (Johnson, 2003; Johnson, et al., 1991), but nowadays can be substituted by DNA analysis (Reiss, et al., 1999a; Shalata, et al., 2000).

The MOCS genes and alternative splicing
The first cDNAs derived from MOCS1 (Reiss, et al., 1998b) carried two open reading frames (ORFs) each coding for a protein homologous to different proteins known to be involved in MoCo synthesis in bacteria (Supp. Fig S3; Rajagopalan and Johnson, 1992) [TO COPYEDITOR: QUERY AUTHOR ON PLACEMENT OF CITE FOR SUPP. FIG. S3]. Later, an alternative splicing pattern was described leading to different monocistronic domain-specific transcripts (Gray and Nicholls, 2000). A full length transcript contains a stop codon in exon 9 (Fig. 3A) and encodes the protein MOCS1A with 385 amino acids homologous to MoaA in E. coli, both carrying the glycine-glycine C-terminus conserved across all examined species except Archea (Supp. Fig. S1A) and shown to be functionally important (Hanzelmann, et al., 2002; Reiss, et al., 1998a). Splice forms 2 and 3 omit the stop codon by skipping exon 9 completely or partially (Fig. 3A), thus elongating the ORF into exon 10, which encodes the MOCS1B domain exclusively expressed as a MOCS1AB fusion protein (Supp. Fig. S1B). The physiological role of the alternative first exons and start codons (Gross-Hardt and Reiss, 2002) as well as other alternative splicing patterns (Arenas, et al., 2009) so far is unknown (Fig. 3B). A processed pseudogene (MOCS1P1) is located on chromosome 16 (NCBI NG_001271).

The MOCS2 gene encodes the small and large subunit of molybdopterin synthase in two overlapping ORFs, i.e. the start codon of the second frame lies within the first frame (Fig. 4 and Supp. Fig. S4) [TO COPYEDITOR: QUERY AUTHOR ON PLACEMENT OF CITE FOR SUPP. FIG. S4]. Both ORFs are shifted relative to each other and thus do not share identical codons. Since the genomic structure of the gene was not completely characterized in the original report (Stallmeyer, et al., 1999a), a leaky scanning mechanism was suggested to allow expression of the second ORF. Within the human genome project an alternative first exon (exon
1b) was identified, which is located between exon 1(a), carrying the start codon of the first ORF, and the original exon 2. The use of the corresponding transcription start leads to a mature transcript rendering the start codon of the second ORF the first translation initiation site on the mRNA (Hahnewald, et al., 2006) thus allowing translation of MOCS2B according to a regular scanning mechanism (Kozak, 1978). MOCS2A, encoded by the first ORF, again carries a conserved glycine-glycine C-terminus (Supp. Fig. S2), whose free accessibility appears to be essential for catalytic function as in the case of MOCS1A (Unkles, et al., 1999).

The gene MOCS3 encodes a protein believed to catalyze both the adenyl transfer and subsequent thiocarboxylation at the C-terminus of the small subunit of molybdopterin synthase (Matthies, et al., 2004), thus providing the sulfur to be incorporated into cPMP (Fig. 1). This gene is located on chromosome 20 and contains no introns. A pseudogene (MOCS3P1) is located on chromosome 14 (NCBI NG_002557). No disease-causing mutation has so far been described in MOCS3.

The GEPH gene

The protein Gephyrin was originally identified by copurification with the mammalian inhibitory glycine receptor and named “bridging protein” due to its proposed function as a receptor-microtubule linker in subsynaptic receptor-clustering (Kirsch, et al., 1993; Prior, et al., 1992). Its
homology to MoCo biosynthesis genes was described in comparison to corresponding sequences from bacteria, fruitflies and plants (Kamdar, et al., 1994; Stallmeyer, et al., 1995). Later, a dual function in receptor clustering and MoCo biosynthesis was confirmed by the investigation of a murine *Geph* knockout model (Feng, et al., 1998), reconstitution assays (Stallmeyer, et al., 1999b) and by the detection of a disease-causing *GEPH* mutation in a deceased MoCo-deficient patient (Reiss, et al., 2001). The Gephyrin protein has two distinct domains, whose function is depicted in Table 1 and Fig. 1.

**Mutations in MoCo deficiency**

With the exception of the above described *GEPH* mutation in a single patient (Reiss, et al., 2001), disease-causing mutations in MoCo deficiency have been described in *MOCS1* and *MOCS2* only (Reiss, 2000; Reiss and Johnson, 2003). Table 2 gives an update of the hitherto identified pathological mutations. The detection rate in biochemically confirmed cases (i.e. elevated sulfite and lowered uric acid levels) is > 99 %. Due to multiple start codons in different exons plus additional alternative splicing events, the nomenclature of mutations in the *MOCS* genes is not trivial. The first mutation reports preceded elucidation of the correct expression mechanisms.
As we know now, the MOCS1B domain is not expressed as a distinct protein but rather as a fusion protein “MOCS1AB” (Fig. 3A) rendering some previously used numbers of corresponding mutation designations on the protein level not conform to nomenclature guidelines. This should be changed as listed in Table 2. For both MOCS1 and MOCS2, we suggest to use the start codon of the first open reading frame for cDNA numbering throughout the complete gene on the basis of a full length transcript (Supp. Figures S1 and S2). In case of multiple first exons the first described should be used to keep changes in nomenclature to a minimum. In case of MOCS1, the “Larin” exon 1a upstream of the first described start codon (in exon 1b) should be addressed explicitly (Table 2), while an identical length of 41 amino acids for the “Larin” trailer (encoded by exon 1a) and the “Reiss” trailer (encoded by exons 1b and 1c) does not interfere with downstream amino acid numbering (Fig. 3B). For the MOCS1AB fusion protein, splice form II should be the basis, i.e. the longer form in comparison to the splice form III protein (Fig. 3).

In case of the MOCS2 gene the nucleotide numbering upstream of the start codon will depend on the specification of the affected protein, i.e. into exon 1a in case of MOCS2A and into exon 1b in case of MOCS2B (Fig. 4). It is noteworthy that compound heterozygous patients carrying one mutation in the A domain and one in the B domain have not been observed in type A (MOCS1) neither in type B (MOCS2), indicating intragenic complementation via the different above described transcripts. An exception is the frameshift mutation c.1000insT located in the MOCS1A ORF (Table 2) and found together with c.1826T>C affecting the MOCS1B domain, which could be explained by a polar effect of the insertion (Fig. 3A). Within Europe a founder effect for most of the repeatedly identified mutations is still visible (Supp. Figure S5).
Animal models and experimental therapies

Knockout mice have been described for Geph (Feng, et al., 1998) and Mocs1 (Lee, et al., 2002). Homozygous Geph -/- mice die within 1 day after birth, but the comparison with Mocs1 -/- mice suggests that this is due to neurological deficits caused by the loss of synaptic clustering of glycine receptors – the second function of Gephyrin besides MoCo biosynthesis. “Pure” MoCo-deficient mice such as the Mocs1 -/- mice die approximately 1 week after birth and are an excellent model for therapeutical studies since they truly reflect the biochemical characteristics of the human disease. The absence of neuropathological findings in the MoCo-deficient mice might be explainable by (i) an improved maternal clearance due to reduced spatial conditions for biochemical gradients and/or (ii) the drastically accelerated progression of the sulfite poisoning (Reiss, et al., 2005). In this animal model, a substitution therapy with cPMP (Fig. 1) had already been described some years ago (Schwarz, et al., 2004).

Using the same animal model, a gene therapy option with AAV vectors has been demonstrated (Hahnewald, et al., 2009; Kugler, et al., 2007). Although the MoCo deficiency phenotype could be completely reverted by just a single injection of AAV capsids carrying a MOCS1 expression cassette, these long term experiments revealed an increased risk for malignancies after recombinant AAV injections. Similar observations have been described by others albeit with different interpretations. While the first corresponding report could not offer an explanation at all
(Donsante, et al., 2001), specific transgenes such as the lacZ reporter have been held responsible for tumorigenesis (Bell, et al., 2006).

Our data do not support a transgene hypothesis since we introduced the same expression cassette that was used for AAV studies also into the germline of MoCo wild-type and deficient mice via microinjection of fertilized oocytes and observed a tumor frequency of only 9 % over 2 years in 46 animals. In contrast, over 20 % of 44 AAV-treated animals, injected either neonatally or 40 days after birth, developed tumors in different organs. After intrahepatic injections predominantly hepatocellular carcinomas were seen, while intravenous applications resulted in a variety of tumors (data not shown).

Clinical studies

Early attempts to ameliorate the symptoms of MoCo deficiency included repeatedly the administration of high levels of inorganic molybdenum, which was found to be inefficient (Bamforth, et al., 1990; Endres, et al., 1988; Johnson, et al., 1980). It has been demonstrated in cell cultures, that this approach is sensible for type III patients with GEPH mutations (Reiss, et
al., 2001). The above cited molybdate treatment of patients, however, preceded gene and mutation identification, which revealed that \textit{GEPH} mutations as the cause of MoCo deficiency are extremely rare. Most likely, patients with other mutations have been treated with molybdate in the published studies. The only patient with \textit{GEPH} mutations described so far deceased before molecular analysis. It should be kept in mind, however, that this type of MoCo deficiency indeed might be curable with high molybdate concentrations. A diet low in sulfur amino acids has in some cases resulted in a significant reduction of abnormal sulfur metabolites although no neurological improvement could be observed (Johnson, et al., 1980).

For decades it had been speculated that at least a part of the MoCo-deficient patients might profit from substitution with precursor Z (now called cPMP, Fig. 1). This pursuit culminated in the decision of an Australian court to allow experimental treatment of “baby Z” (as it was called in the popular press) with a cPMP preparation tested before exclusively in mice (Veldman, et al., 2010). Before, animal studies had ruled out convincingly any adverse effects (Schwarz, et al., 2004). The affected baby was homozygous for the MOCS1B mutation G588R (Table 2) and thereby classified as type A defective in cPMP synthesis (Fig. 2). Cranial ultrasound examinations at 1 month showed cerebral atrophy and loss of gray/white-matter differentiation, Intravenous replacement therapy with cPMP started on day 36 by extrapolating the dose that had been most efficient in the mouse model (Schwarz, et al., 2004). Since the cPMP infusions were well tolerated and triggered no observable adverse effects, they were continued on a daily basis with occasional dosage adjustment. Within a few days normalization of the previously markedly elevated levels of S-sulfocysteine and thiosulfate were achieved. Within 2 days the infant became more alert and at an age of 18 months she is clinically free of seizures. In summary, the
substitution therapy cannot reverse cerebral injury observed before commencing cPMP supplementation. However, ongoing neurotoxicity and further deterioration definitely can be excluded. Four more type A patients are currently cPMP-treated with similar outcome (Günter Schwarz, personal communication).

Future prospects

The availability of a causative treatment immediately raised the question about screening possibilities for MoCo deficiency. A practicable (and affordable) way to the early identification of curable patients might be the routine determination of the ratio of uric acid and xanthine concentrations, which in case of lowered values and in the absence of other immediate explanations should be followed by a test for elevated sulfite levels. If the latter confirms a lack of active MoCo, the precise type of the deficiency must be determined either biochemically or by genetic testing. Although the ethnic origin of a patient often renders specific mutations to be found more likely than others (Supp. Figure S5), the speed of sequencing complete genes (if not genomes) reached by now suggests a complete analysis of MOCS1 and MOCS2 in a first step, which results in a mutation detection rate of more than 99 percent. Only in the case of negative results up to here, sequencing of the genes GEPIH and MOCS3 appears to be indicated.
Despite the demonstration of successful treatment possibilities for type A in clinical studies and for type C in cell culture experiments, type B deficiencies so far appear to be incurable. The relative instability of molybdopterin (with or without molybdenum) hampers substitution therapy analogue to cPMP supplementation. Theoretical options still to be explored are enzyme replacement therapy with MOCS2 proteins or functional sulfite oxidase and safe avenues of gene therapy. The latter might include the use of AAV vectors, if parameters such as titer, serotype and route of application are optimized in terms of a minimal malignancy risk.

Acknowledgments

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References


Reiss J, Johnson JL. 2003. Mutations in the molybdenum cofactor biosynthetic genes MOCS1, MOCS2, and GEPH. Hum Mutat 21(6):569-76.


Legends to Figures

**Figure 1.** Biosynthesis of MoCo via an ancient pathway common to all free-living species and types of diseases as a consequence of mutations in the different genes. MOCS1A belongs to the superfamily of S-adenosylmethionine-dependent radical enzymes, members of which catalyze the formation of radicals by a protein-bound [4Fe-4S] cluster (Hanzelmann, et al., 2004). It is speculated that the B domain of the MOCS1AB fusion protein might function as a radical acceptor (Teschner, et al., 2010). The two MOCS2 proteins A and B are subunits of molybdopterin synthase incorporating sulfur groups delivered by the MOCS3 sulfurylase (Matthies, et al., 2004). Finally, molybdenum is attached to these sulfur groups in a two step-reaction catalyzed by the *GEPH*-encoded two domain-protein Gephyrin (Kuper, et al., 2004; Llamas, et al., 2006).

**Figure 2.** Metabolites influenced by MoCo deficiency.

**Figure 3.** Alternative splicing of the *MOCS1* transcript. (A) Use of the first stop codon in exon 9 leads to an active MOCS1A protein with the strictly conserved and functionally obligate two glycine residues at the C-terminus in splice form I. Splice forms II and III lead to a fusion protein with an inactive A domain and the functional B domain. (B) The exons 1a and 1b are mutually exclusive. The two different trailers of the most common Larin and Reiss variants have an identical length of 41 amino acids.
Figure 4. Expression of the *MOCS2* gene. Exons 1a and 1b are mutually exclusive and lead to the expression of two distinct proteins via spliceforms I and III, respectively. Spliceform II cannot be found in the databases anymore and probably was an artifact. The open reading frames of the small and large subunit of molybdopterin synthase overlap in exon 3. The essential Gly-Gly C-terminus of MOCS2A is in red color.
Table 1. Nomenclature of homologous genes or protein domains, respectively, involved in MoCo synthesis among different species

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¹Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence GenBank AJ224328.1 for MOCS1 (see also Supp. Fig. S1) and Genbank AF091871.1 for MOCS2 (see also Supp. Fig. S2), according to journal guidelines ([www.hgvs.org/mutnomen](http://www.hgvs.org/mutnomen)). The initiation codon is codon 1.
This mutation affects only the Larin variant (see also Fig. 3B), which is not included in the reference sequence, but in Supp. Fig. S1.

Cecile Acquaviva, Service Maladies Hereditaires du Metabolisme, Centre de Biologie Est – Groupement Hospitalier Est, 59, bd Pinel – 69677 BRON cedex
A, splice form I: bicistronic transcript - active MOCS1A
B, Larin - variant

splice form II: monocistronic transcript - inactive MOCS1A and active MOCS1B

splice form III: monocistronic transcript - inactive MOCS1A and active MOCS1B

Reiss - variant

Gross-Hardt - variant

Arenas - variant
MOCS2A

spliceform I

ATG

TGA

R Q E Y V L G D Q L L V L Q P G D E I A V I P P I S G G X
cgtcagataatctcgctttgagcttgagctcggatagctgcggacatattgcgtcatgtttttag

 spliceform III

MOCS2B

ATG

TGA

104x41mm (600 x 600 DPI)
Supp. Figure S1. Alignment of the proteins MOCS1A (A) and MOCS1AB (B). Conserved amino acid positions are shaded. The essential Cys clusters (Menendez, et al., 1996) are boxed.
**Supp. Figure S2.** Alignment of the proteins MOCS2A (A) and MOCS2B (B). Conserved amino acid positions are shaded.
Reiss et al., *Human Mutation*

Larin-variant (exon 1a)

1    atggcggcgcggccacgtgctccggatgcgtcgccggcgtttctgaggtccagcgcccggagc
    M A A R P L S R M L R R L R S S A R S 20

61   tgcaagctcagggctcgggttgacccagcctgccccggagctcgccgcagctgctcctc
c S S G A P V T Q P C P G E S A R A A S 40

121  gag...

E 41

Reiss-variant (exon 1b and c)

1    atgtgaagagttggaagctccgcacagatgtcagagtaagggaggggcaggcgggttct
    M W K S W K L R T D V R V R E G A G G S 20

61   ccttgctcctctccagccgggttgcacgagggcccatctcctcctcgttctgtctctc
P C A S S Q P G S R G P C F L P G L S S 40

121  cag...

Q 41

Both variants (exons 1d – 10)

124 ...gaggtgtcagcgcggagcagttctcgcggagcatgcgcgccttcctgcgccttc
e V S R R R Q F L R E H A A P F S A F 60

181  ctcacagacagcttccgcggcagcagcagctcactgcgtccctccacagagagtcgc
l T D S F G R Q H S Y L R I S L T E K C 80

241  accctcagatgtcagttgcagccgggccggaggggtctgaccccaacgaccaac
n L R C Q Y C M P E E G V P L T P K A N 100

301  cttctgaccacagagagtagctcctagccctcgcggctctttgttagggaagccatctgac
l L T T E E I L T L A R L F V K E G I D 120

361  aagatccggttcacaggtgagagcagcgtttatccggccggacgtggttggacattgtggcc
k I R L T G G E P L I R P D V V D I V A 140

421  cagcttcacagcggctggagggctgagcaccataagggtttacaccacaatggcatcaacctg
q L Q R L E G L R T I G V T T N G I N L 160
Reiss et al., Human Mutation

481  gcccggctactgcccaagctttgctcagttgctgaccatcaacactcagcctggac
     A R L L P Q L Q K A G L S A I N I S L D 180

541  acccttgtgcctggtaagtttgagttcattgtgccgacgaaggttctccacaaggtcatag
     T L V P A K F I V R R K G F H K V M 200

601  gaggccatcccaacagggcatcagctggctgctacaacaggtgaaactgtgtggtg
     E G I H K A I G L Y N P V K V N C V V 220

661  atgcgaggcttttaacagaggataactcctggactttgcgccttgactgaagggcctccc
     M R G L N E D E L D F A A L T E G L P 240

721  ctggatgtgcgcttcataagagatactctctgcgcacgtgggacggcttggaagaa
     L D V R F I E Y M P F D G N K W N F K 260

781  atgtctagctataagagatctctacactgctgcagcagctgcagacttgaaggaacagcctggac
     M V S Y K E M L D T V R Q W P E L E K 280

841  gtgcagagggaggaatccagcacagccagcagccagccagctctattaatatcccttgctccaaagggcaag
     V P E E E S S T A K A F K I P G F Q G Q 300

901  atcagctcctcctacatcataagctgtgtgaattttctgctgacgtcgtgctggaagaa
     I S F I T S M S E H F C G T C N R L R I 320

961  acagctgatgggaacctcaaggtctgccttggaaactctgaggtatccctgcgggat

1021 cacctgcgagctgggctctgctgacagtgaattttcctgcctgtcagttgggtgacggtcgtcgtggtgac
     H L R A G A S E Q E L L R I I G A A V G 360

1081 aggaagaagcggcagcatcagccagctgtctctcttcgttatcctggcagctggtgtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggtggt
Reiss et al., Human Mutation

Supp. Figure S3. Sequences of the MOCS1 cDNA and the proteins MOCS1A and MOCS1AB. Nucleotide numbering refers to the full length transcript including the complete exon 9 (splicefform I). Mutations in exon 1a should be explicitly marked “Larin variant” since they are not included in the reference sequence (GenBank AJ224328.1). Mutations in exon 10 affect the MOCS1AB fusion protein, which should be specified in the nomenclature for the predicted effect.
Reiss et al., Human Mutation

Supp. Figure S4. Sequences of the MOCS2 cDNA (spliceform I) and the proteins MOCS2A (upper one letter code) and MOCS2B (lower one letter code).
**Supp. Figure S5.** Geographical distribution of MOCS1 and MOCS2 mutations found in more than one family within Europe. Each box represents one allele. For each family only one index patient was counted.