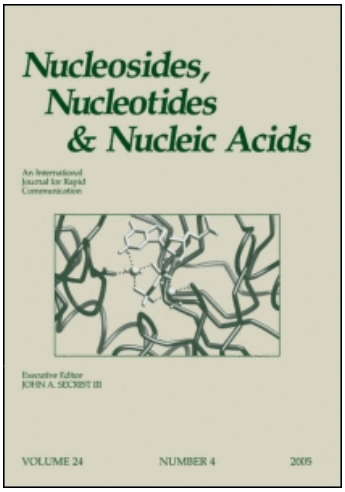

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A TURKISH CASE WITH MOLYBDENUM COFACTOR DEFICIENCY

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□ *Molybdenum cofactor deficiency (MIM 252150) is a rare progressive neurodegenerative disorder with about 100 cases reported worldwide. We have identified a male with molybdenum cofactor deficiency and analyzed the molybdenum cofactor synthesis (MOCS)1 gene, MOCS2 gene, MOCS3 gene and GEPH gene. We homozygously identified the CGA insertion after A666 of the MOCS1 gene which produces arginine insertion at codon 222 of MOCS1A. The parents, his brother and his sister who did not have any symptoms were heterozygous for the same mutation. This region was highly conserved in various species. The N-terminal part of MOCS1 a protein is suggested to form the central core of the protein and be composed of an incomplete [(alpha/beta)6] triosephosphate isomerase (TIM) barrel with a lateral opening that is covered by the C-terminal part of the protein. The insertion is located in the loop connecting the fifth beta strand to the sixth alpha helices of the TIM barrel structure. This arginine insertion would induce the conformation change and the lack of the activity.*

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Keywords Molybdenum cofactor deficiency; MOCS1 gene; Triosephosphate isomerase barrel; MOCS1A; Mutation

INTRODUCTION

Molybdenum cofactor deficiency (MIM 252150) is a rare progressive neurodegenerative disorder with about 100 cases reported worldwide.[1] The clinical manifestations are severe seizures unresponsive to any therapy in the neonatal period, abnormal tone and opisthotonus, severe mental retardation, craniofacial dysmorphic alterations and lens dislocation.[2] Molybdenum cofactor deficiency results in a loss of all molybdoenzyme activities (sulfide oxidase, xanthine dehydrogenase, and aldehyde oxidase). The lack of sulfite oxidase activity causes increased urinary excretion of sulphite, thiosulphate, taurine, S-sulphocysteine, and low plasma cystine and the lack of xanthine dehydrogenase activity causes xanthinuria and hypouricemia. Recently, the genes related with molybdenum cofactor synthesis (MOCS), MOCS1 gene, MOCS2 gene, MOCS3 gene, and gephyrin (GEPH) gene, were cloned and the responsible mutations for the disease have been identified.[3–7] We have identified a novel mutation in the MOCS1 gene of a male with molybdenum cofactor deficiency.

MATERIALS AND METHODS

Case Report

The patient, born to consanguineous Turkish parents, was admitted at the age of 7 years. Out of 7 siblings, 3 had the same following symptoms the patient. One of the siblings was diagnosed with molybdenum cofactor deficiency in France. He had mental and motor retardation, dystonic movements, and spastisity. His first convulsion was at the age of 4 or 5 months old. His developmental milestones were delayed at all ages. We diagnosed him with molybdenum cofactor deficiency. DNA analysis of the genes related with molybdenum cofactor synthesis was performed for the parents, his brother and his sister who did not have any symptoms and the patient.

Methods

After genomic DNA was isolated from peripheral white blood cells and subjected to the PCR reactions, direct sequencing for the coding regions of the genes, *MOCS1*, *MOCS2*, *MOCS3*, and *GEPH*, was performed. Restriction fragment length polymorphism (RFLP) analysis was performed for the detection of the genotype of the 666insCGA in *MOCS1*. For the detection of

the genotype, a part of *MOCS1* gene including the mutation was amplified by PCR using the forward primer 5′-CAGGTGAACTGTGTGGTGATGCGT-3′ and the reverse primer 5′-CCATACCCAGTGGGTGAGCCACACTATG-3′. The PCR amplified a 201-bp fragment of genomic DNA, including nucleotide position 666. By setting T instead of A at the 3′ end of the forward primer, a new Taq I digestion site was created in the PCR product. Upon digestion of the PCR product with the restriction enzyme Taq I, only the PCR product that has a CGA insertion at position 666 in *MOCS1* gene is cleaved into 177-bp and 24-bp fragments.

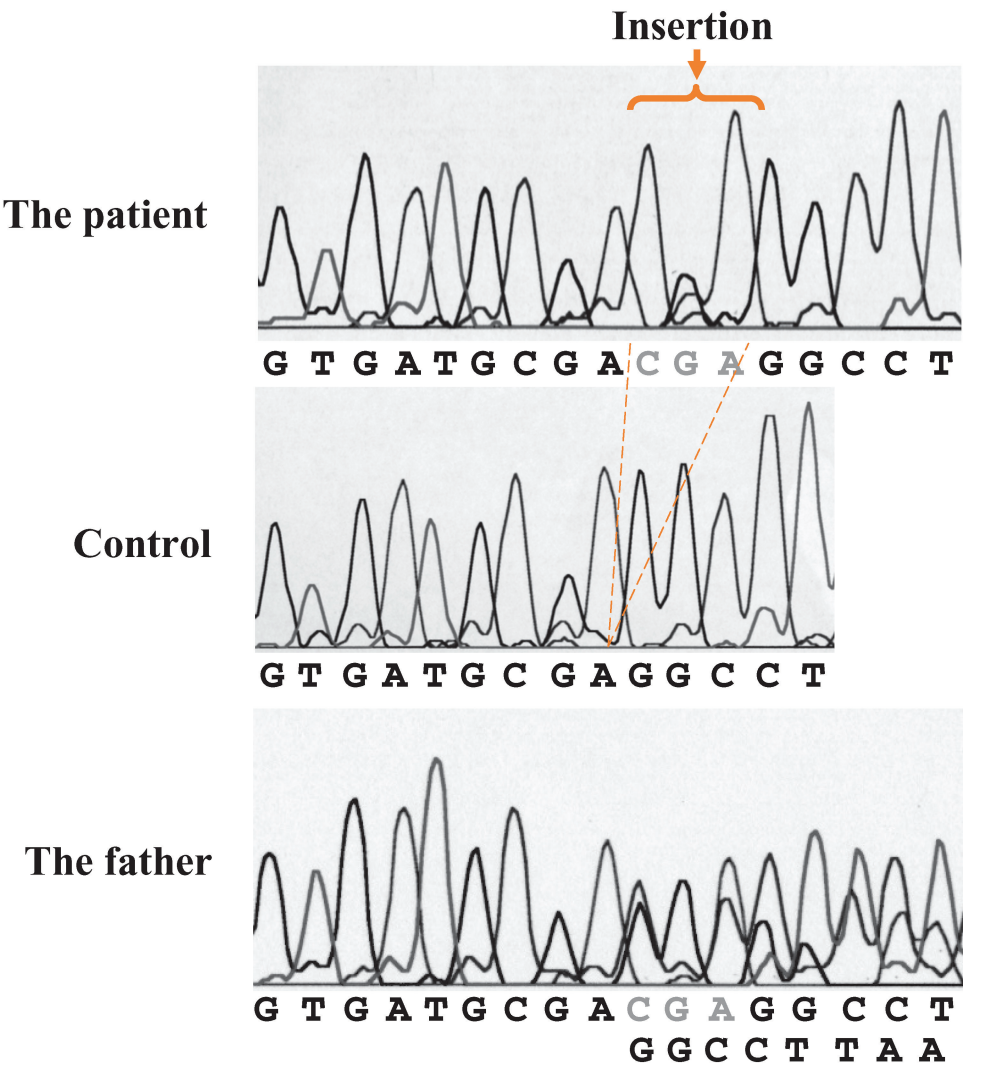

FIGURE 1 The mutation in the MOCS1 gene of the patient, the father and the control. The sequences in the mother, the brother, and the sister were similar to the sequence in the father (not shown).

RESULTS

We amplified and sequenced all the coding regions of the genes related with molybdenum cofactor synthesis of the patient, the parent, his brother, and sister by PCR. Within the entire coding region, a CGA insertion at nucleotide position 666 was identified in the patient (Figure 1). The nucleotide insertion results in an arginine insertion at codon 222. Genomic DNA from the patient, the parents, two siblings and a control subject was submitted to the PCR and the procedure of digestion with Taq I followed by RFLP analysis, as described in earlier. The RFLP analysis revealed that the patient was homozygous, while the parents and two siblings were heterozygous for the CGA insertion at nucleotide position 666 (Figure 2). This insertion was not found in the 42 control alleles.

DISCUSSION

MOCS1 gene, the bicistronic gene, encodes two proteins, MOCS1A and B. In the *MOCS1* gene of the patient with molybdenum cofactor deficiency, we identified the CGA insertion after A666 which resulted in arginine insertion at codon 222 of MOCS1A. The parents, his brother and his sister who did not have any symptoms were heterozygous for the same mutation. MOCS1A belongs to the S-adenosylmethionine dependent radical enzyme superfamily. MOCS1A contains two highly conserved cysteine motifs near the N terminus and C terminus, ligating FeS clusters.[8,9] This insertion is not located in close proximity to the conserved cysteine motifs. The

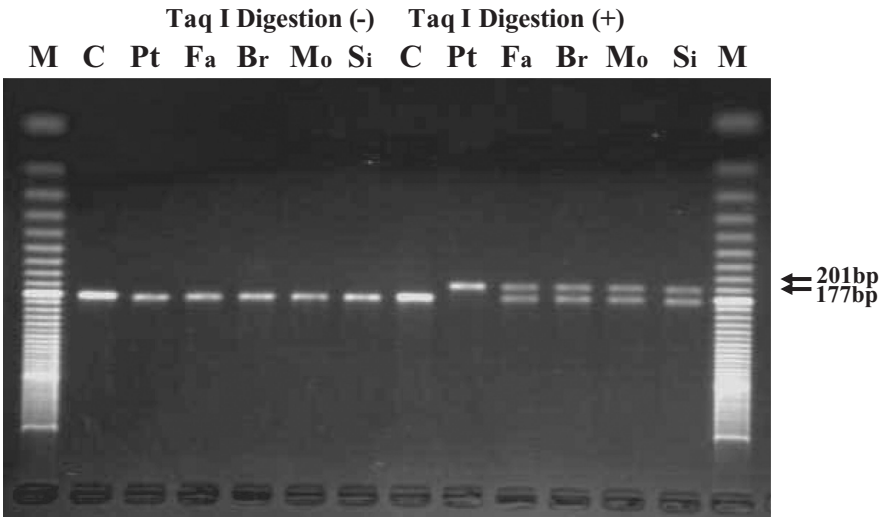

FIGURE 2 RFLP analysis for the detection of the mutational genotype (M: Marker, C: Control, Pt: Patient, Fa: Father, Br: Brother, Mo:Mother, Si: Sister).

N-terminal part of MOCS1A protein is suggested to form the central core of the protein and be composed of an incomplete $[(\alpha/\beta)6]$ triosephosphate isomerase (TIM) barrel with a lateral opening that is covered by the C-terminal part of the protein.[8] The insertion is located in the loop connecting the fifth beta strand to the sixth alpha helices of the TIM barrel structure. This arginine insertion would induce the conformation change and the lack of the activity.

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