Biochemical and genetic aspects of mevalonate kinase and its deficiency
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Chapter 5

Molecular basis of classical mevalonic aciduria and the hyperimmunoglobulinaemia D and periodic fever syndrome: High frequency of 3 mutations in the mevalonate kinase gene


The classical type of mevalonic aciduria (MA; MIM 251170) is a rare autosomal recessive metabolic disorder characterized by psychomotor retardation, failure to thrive, hepatosplenomegaly and anemia. In addition, patients suffer from recurrent episodes of fever, associated with lymphadenopathy, arthralgia, gastrointestinal problems and skin rash. The disorder is caused by deficient activity of mevalonate kinase (MK). As a consequence of the MK deficiency, high levels of mevalonic acid are present in plasma and urine from patients [1]. Recently, mevalonic aciduria was also recognized in patients with hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS; MIM 260920), who also suffer from recurrent episodes of fever [2, 3]. The mevalonic aciduria in HIDS patients, however, was moderate and observed only during the febrile crises. MK enzyme activity was decreased, but not fully deficient, varying between 1% and 4% residual activity [2]. The diagnostic hallmark of HIDS is a constitutively elevated level of serum IgD, usually accompanied with elevated levels of serum IgA [4]. However, we recently identified patients with the classical HIDS phenotype and MK deficiency but normal serum IgD levels [2].

Both syndromes are caused by mutations in the gene encoding MK. In HIDS one missense mutation, 1129G>A, was common to most patients analyzed thus far [2, 5]. Most patients were compound heterozygotes. At present, mutations in eight MA patients have been characterized [6-9]. In three patients an 803T>C mutation was identified for which a Mennonite ancestry was suggested [8]. This allele was also identified in two additional HIDS patients, suggesting a high frequency of this mutation.

We describe here the frequency of these two and a third common mutation in the MK gene identified in eight new HIDS patients and calculate the allele frequency of these mutations in all reported HIDS and MA patients. In addition, we make a comparison between the genotypes of HIDS and MA patients.

Materials and Methods
All patients studied were clinically diagnosed with HIDS and had strongly decreased activities of MK as measured in fibroblasts and/or lymphocytes making use of $^{14}$C-labeled mevalonate [10]. Mutation analysis was performed on cDNA as described previously [9].

Results and Discussion
Previous studies suggested that the 1129G>A mutation in the MK gene was the most common cause of HIDS. We sequenced eight additional HIDS patients and identified nine 1129G>A alleles. One patient was homozygous; this was confirmed by sequencing parental material. In addition, we identified four 803T>C alleles and one 59A>C allele. Both alleles had previously been reported in other HIDS and MA patients, indicating a high frequency of these alleles. Table 1 summarizes the frequency of these alleles in our patients and patients diagnosed in other laboratories. The table includes only data of one affected member per family in those cases where more members have been identified.

The 1129G>A mutation has an allele frequency of 52% among HIDS patients. At this moment, only one HIDS patient has been described who did not carry this allele [5]. None of the MA patients carried the 1129G>A allele, strongly suggesting that this mutation is responsible for the residual MK activity measured in HIDS fibroblast lysates [2]. Heterologous expression of this allele as a GST-MK fusion protein in *Escherichia coli* revealed reduced enzyme activity. In addition, immunoblot analysis showed a profound
deficiency of the protein in lysates of skin fibroblasts of HIDS patients, suggesting instability of the product of this allele in vivo [2].

Table 1. Frequency of three common mutations in the MK gene in HIDS and MA patients.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of alleles in HIDS</th>
<th>Number of alleles in MA</th>
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<tbody>
<tr>
<td>1129G&gt;A</td>
<td>14 (24 alleles)</td>
<td>0 (6 alleles)</td>
</tr>
<tr>
<td>803T&gt;C</td>
<td>5 (18 alleles)</td>
<td>2 (10 alleles)</td>
</tr>
<tr>
<td>59A&gt;C</td>
<td>3 (18 alleles)</td>
<td>0 (6 alleles)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allele</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1129G&gt;A</td>
<td>52%</td>
</tr>
<tr>
<td>803T&gt;C</td>
<td>14%</td>
</tr>
<tr>
<td>59A&gt;C</td>
<td>7%</td>
</tr>
</tbody>
</table>

The estimated frequency of the 803T>C allele among both HIDS and MA patients is 17%. Heterologous expression of this mutant allele in E. coli resulted in strongly reduced MK enzyme activity. Moreover, immunoblot analysis revealed low protein levels in an MA patient homozygous for this allele [9]. The fact that this severely affected MA patient died at an early age suggests that the frequency of this allele might be underestimated owing to lethality in utero. This allele was also identified in the only HIDS patient without the 1129G>A mutation, which suggests that the second mutation identified in this patient, 500C>T, leads to the HIDS phenotype. Heterologous expression of the resulting mutant enzyme and protein level analysis by immunoblotting will be needed to determine the effect of this 500C>T mutation on the enzyme.

The third common allele, 59A>C, which encodes an inactive protein when expressed in E. coli, has a frequency of 7% among HIDS and MA patients.

References