A genotype-phenotype correlation in HNPCC: strong predominance of msh2 mutations in 41 patients with Muir-Torre syndrome

E Mangold, C Pagenstecher, M Leister, M Mathiak, A Rütten, W Friedl, P Propping, T Ruzicka, R Kruse

Muir-Torre syndrome (MTS; MIM 158320) is an autosomal dominant predisposition to skin tumours and various internal malignancies. Clinical criteria for a diagnosis of MTS are the synchronous or metachronous occurrence of at least one sebaceous gland neoplasm and at least one internal neoplasm in a patient (regardless of the family history). The sebaceous gland neoplasias comprise adenomas, epitheliomas (sebaceomas), and carcinomas. In contrast, the frequent sebaceous gland hyperplasia is not indicative of MTS. According to Schwartz and Torre, the sebaceous neoplasias precede the internal neoplasias or are concurrent with them in 41% of MTS patients. As sebaceous gland neoplasias are rare, MTS should always be suspected when a sebaceous tumour has been diagnosed. Cystic sebaceous neoplasia is probably the most sensitive marker for this tumour predisposition syndrome. Colorectal cancer is by far the most common internal malignancy in MTS patients. The spectrum of internal malignancies in MTS is similar to the various tumour entities observed in hereditary non-polyposis colorectal cancer (HNPCC; MIM 114500). HNPCC is an autosomal dominant cancer predisposition syndrome characterised by early onset of colorectal cancer and other associated tumours. Several genes underlying HNPCC which are involved in DNA mismatch repair (MMR) have been identified within the last decade. Germline mutations in the DNA MMR genes were detected in a high proportion of MTS patients, demonstrating that MTS most often represents a phenotypic variant of HNPCC. Due to the underlying genetic mechanisms of tumourigenesis, tumours of these MTS patients exhibit high microsatellite instability (MSI-H), the characteristic feature of HNPCC tumours. Microsatellite analysis in tumour tissue of MTS patients therefore provides a useful tool to pre-select patients for mutation analysis in DNA MMR genes. Immunohistochemical testing for expression of the MSH2 and MLH1 proteins in skin tumour tissue is an alternative reliable screening method with high predictive value for the diagnosis of DNA mismatch repair deficient MTS (HNPCC).

A diagnosis of HNPCC in an MTS patient is of major importance for both the patient and his/her close relatives, as all family members who inherited the DNA MMR defect have a substantially higher risk for HNPCC malignancies and should therefore undergo regular cancer surveillance examinations. Identification of the underlying DNA MMR germline mutation in the index patient enables predictive genetic testing of his/her family members at risk.

To date, DNA MMR gene mutations in MTS patients have been reported in both the MSH2 and MLH1 genes. While the proportions of MLH1 and MSH2 mutations in HNPCC are almost equal (ICG-HNPCC mutation database, http://www.nfdht.nl), in MTS the vast majority of mutations have been identified in MSH2. This suggests a genotype correlation for the Muir-Torre phenotype among HNPCC patients.

The aim of this study was to further support this genotype-phenotype correlation in HNPCC. We determined the DNA mismatch repair gene mutations in the DNA MMR gene spectrum of a large MTS patient sample after pre-selection by examination for MSI and immunostaining in tumour tissue. For this purpose we extended our previously reported sample of 15 MTS patients to a total of 41 patients for mutation analysis in DNA MMR genes. Thirty seven of these patients had met the Bethesda criteria for HNPCC, nor do their families. Applying only the current Bethesda criteria would have resulted in these patients being overlooked. The Muir-Torre phenotype should therefore be regarded as a highly specific indicator for hereditary DNA mismatch repair deficiency. Even in patients not meeting the Bethesda criteria, a sebaceous neoplasm makes diagnosis of HNPCC likely.

Key points

- Sebaceous gland neoplasias are the characteristic cutaneous manifestation of Muir-Torre syndrome (MTS), a phenotypic variant of hereditary non-polyposis colorectal cancer (HNPCC).
- We performed mutation analysis in 41 unrelated index patients diagnosed with Muir-Torre syndrome or a sebaceous neoplasm. Thirty seven of these patients had been pre-selected for DNA mismatch repair deficiency in tumour tissue following proof of either high microsatellite instability or loss of MSH2/MLH1 protein expression, or both. In 27 of the 41 patients, we detected germline mutations in the DNA mismatch repair genes MSH2 and MLH1 (mutation detection rate of 66%); three mutations were large genomic deletions.
- In contrast to HNPCC patients without the MTS phenotype, significantly more MSH2 mutations were detected among the MTS patients: 25 (93%) mutations were located in MSH2 compared to only two in MLH1. Our findings should have consequences for mutation detection protocols in MTS patients or HNPCC patients who have family members with MTS.
- Interestingly, six (22%) of the mutation carriers do not meet the Bethesda criteria for HNPCC, nor do their families. Applying only the current Bethesda criteria would have resulted in these patients being overlooked. The Muir-Torre phenotype should therefore be regarded as a highly specific indicator for hereditary DNA mismatch repair deficiency. Even in patients not meeting the Bethesda criteria, a sebaceous neoplasm makes diagnosis of HNPCC likely.

Abbreviations: DHPLC, denaturing high performance liquid chromatography; HNPCC, hereditary non-polyposis colorectal cancer; MLPA, multiplex ligation-dependent probe amplification; MMR, mismatch repair; MSI-H, high microsatellite instability; MTS, Muir-Torre syndrome; PTT, protein truncation test; SSCP, single strand conformation polymorphism.
patients. Either the patients were diagnosed with MTS by clinical criteria or MTS was suspected due to the occurrence of at least one sebaceous neoplasm. To our knowledge, this is the largest sample of MTS patients screened for DNA MMR mutations to date.

METHODS
Selection of patients included in mutation screening
Screening for germline mutations in MSH2 and MLH1 was performed in 41 unrelated index patients. Of the 41 patients, 37 met the diagnostic criteria for MTS. In four patients, only one sebaceous neoplasm had been diagnosed, raising the suspicion of MTS.

Of the 41 index patients, 40 originated from a sample of patients who had been ascertained on the basis of both a sebaceous skin neoplasm and an internal malignancy, or on a sebaceous skin neoplasm only. Ascertainment of these patients had been carried out irrespective of family history or age at onset of tumours. Only one index patient (patient 62) is a member of a known HNPCC family which was originally ascertained following early manifestation of multiple colorectal cancers.

Pre-screening analysis of sebaceous tumour tissue for MSI-H and for loss of MLH1 and MSH2 protein expression was performed as previously reported. In 37 patients, an underlying DNA MMR gene defect was indicated by tumour tissue analysis, either microsatellite analysis or immunohistochemistry, or both. These 37 patients and a further four patients, in whom a clinical diagnosis of MTS had been made but for whom no tumour tissue was available, were included in mutation analysis.
in the mutation screening. Fifteen of these index patients were described previously, while 26 patients are reported here for the first time (table 1).

Written informed consent was obtained from all patients included. The study was approved by the ethical committees of the University Hospitals in Dusseldorf and Bonn.

**Search for germline mutations in MSH2 and MLH1**

Peripheral blood was drawn from all index patients to extract genomic DNA by a standard salting out procedure.21 The peripheral blood was drawn from all index patients to extract genomic DNA by a standard salting out procedure.21 The frequency between patients with the MTS phenotype and patients without the MTS phenotype was determined by using the protein truncation test (PTT), heteroduplex analysis, or single strand conformation polymorphism (SSCP) analysis according to Kruse et al.22 In 14 patients, the results of immunohistochemical analysis indicated localisation of a mutation in the MSH2 gene. Only in one patient (patient 810) was neither loss of MSH2 nor loss of MLH1 expression found; this patient was carriers of variant C697F. Immunohistochemical tissue analysis in patient 62 revealed loss of MSH2 expression. This finding further supports the assumption that variant C697F is indeed disease causing. As members were found to be carriers of variant C697F.

**RESULTS**

We searched for a germline mutation in MSH2 and MLH1 in 41 patients either diagnosed with MTS according to the clinical criteria or with suspicion of MTS due to the occurrence of a sebaceous neoplasia. A total of 37 of these patients had been pre-selected by examination of tumour tissue for loss of DNA MMR protein expression and/or high microsatellite instability. In 27 of the 41 patients, germline mutations were identified, corresponding to a mutation detection rate of 66%. Sixteen of these mutations are described in the context of the Muir-Torre syndrome for the first time in this study; seven mutations are novel and not listed in the ICG-HNPPC database (table 2).

A total of 24 mutations were identified in the 37 patients pre-selected by tumour tissue analysis. The tumour tissue of MSH2 mutation carriers was available for immunohistochemistry in 14 patients. In 13 patients, the results of immunohistochemical analysis indicated localisation of a mutation in the MSH2 gene. Only in one patient (patient 810) was neither loss of MSH2 nor loss of MLH1 expression found; this patient carried a missense variant in MSH2. A mutation was detected in three out of four patients with MTS from whom no tumour tissue was available for pre-screening.

Twenty five (93%) of the identified mutations are predicted to lead to a truncated protein and therefore have to be regarded as definitely disease-causing genetic alterations. The majority of these are small point mutations: a total of 12 frameshift mutations, eight nonsense mutations, and two alterations at the highly conserved splice site positions were identified. Three large genomic deletions encompassing several exons were detected by additional deletion screening. Two MSH2 missense mutations of unknown relevance were identified, R524P (patient 810) and C697F (patient 62). No other possible disease-causing variants in MSH2 or MLH1 were found in these patients. In family 62, DNA samples of four affected family members from two generations were analysed for the missense mutation and all affected family members were found to be carriers of variant C697F. Immunohistochemical tissue analysis in patient 62 revealed loss of MSH2 expression. This finding further supports the assumption that variant C697F is indeed disease causing. As regards patient 810, no other affected family members were available for segregation analysis and immunohistochemistry.

**Table 2 Mutations detected in 27 index MTS patients**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Gene</th>
<th>Exon</th>
<th>Mutation</th>
<th>Effect</th>
<th>MSI status</th>
<th>MMR protein loss at IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>555 (MTS-23)</td>
<td>MSH2</td>
<td>1 to 6</td>
<td>c.1228delC</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>554 (MTS-21)</td>
<td>MSH2</td>
<td>1</td>
<td>c.145delGT</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>593 (MTS-10)</td>
<td>MSH2</td>
<td>2</td>
<td>c.289C&gt;T</td>
<td>Q97X</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>162 (MTS-9)</td>
<td>MSH2</td>
<td>3</td>
<td>c.2015delT</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>726 (ST-62)</td>
<td>MSH2</td>
<td>3</td>
<td>c.923_933dupG</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>278 (ST-55)</td>
<td>MSH2</td>
<td>5</td>
<td>c.862C&gt;T</td>
<td>Q288X</td>
<td>MSI-H</td>
<td>MSH2</td>
</tr>
<tr>
<td>122 (ST-33)</td>
<td>MSH2</td>
<td>5</td>
<td>c.942+3A&gt;T</td>
<td>Alteration of splicing</td>
<td>MSI-H</td>
<td>NT</td>
</tr>
<tr>
<td>761 (ST-63)</td>
<td>MSH2</td>
<td>7</td>
<td>c.1592C&gt;T</td>
<td>Q397X</td>
<td>ND</td>
<td>MSH2</td>
</tr>
<tr>
<td>533 (ST-45)</td>
<td>MSH2</td>
<td>7</td>
<td>c.2193C&gt;T</td>
<td>Q465X</td>
<td>MSI-H</td>
<td>MSH2</td>
</tr>
<tr>
<td>788 (ST-33)</td>
<td>MSH2</td>
<td>8</td>
<td>c.1373T&gt;G</td>
<td>L458X</td>
<td>ND</td>
<td>MSH2</td>
</tr>
<tr>
<td>631 (MTS-18)</td>
<td>MSH2</td>
<td>9, 10</td>
<td>c.1884_1888delGGAAA</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>NT</td>
</tr>
<tr>
<td>398 (MTS-24)</td>
<td>MSH2</td>
<td>10</td>
<td>c.1217_1220del</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>132 (MTS-24)</td>
<td>MSH2</td>
<td>11</td>
<td>c.597delA*</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>NT</td>
</tr>
<tr>
<td>167 (MTS-24)</td>
<td>MSH2</td>
<td>11</td>
<td>c.1700_1703delAAAC*</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>133 (MTS-24)</td>
<td>MSH2</td>
<td>12</td>
<td>c.1251delT*</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>MSH2</td>
</tr>
<tr>
<td>655 (ST-29)</td>
<td>MSH2</td>
<td>12</td>
<td>c.2005-2T&gt;Ct</td>
<td>Alteration of splicing</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>851 (MTS-8)</td>
<td>MSH2</td>
<td>13</td>
<td>c.2015delT*</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>NT</td>
</tr>
<tr>
<td>62 (MTS-7)</td>
<td>MSH2</td>
<td>13</td>
<td>c.1090_1091delGG</td>
<td>Frameshift</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>677 (ST-29)</td>
<td>MSH2</td>
<td>13</td>
<td>c.2113C&gt;T</td>
<td>R711X</td>
<td>MSH2</td>
<td>MSH2</td>
</tr>
<tr>
<td>628 (ST-27)</td>
<td>MSH2</td>
<td>14</td>
<td>c.2228C&gt;G</td>
<td>R743X</td>
<td>MSH2</td>
<td>MSH2</td>
</tr>
<tr>
<td>762 (MTS-9)</td>
<td>MLH1</td>
<td>15</td>
<td>c.150_151insG</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>762 (MTS-9)</td>
<td>MLH1</td>
<td>15</td>
<td>c.150_151insG</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>762 (MTS-9)</td>
<td>MLH1</td>
<td>15</td>
<td>c.150_151insG</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>762 (MTS-9)</td>
<td>MLH1</td>
<td>15</td>
<td>c.150_151insG</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
<tr>
<td>762 (MTS-9)</td>
<td>MLH1</td>
<td>15</td>
<td>c.150_151insG</td>
<td>Large deletion</td>
<td>MSI-H</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Mutation (according to current nomenclature) in this patient diagnosed with MTS or suspected MTS was reported previously.*15 16 21 22 Frameshift mutation not listed in the ICG-HNPPC database (http://www.mlh1.nl). IHC, immunohistochemistry; ND, not detected; NT, no tumour tissue available.

**Statistical analysis**

Fisher’s exact test was applied in order to test the null hypothesis of no difference in MSH2 and MLH1 mutation frequency between patients with the MTS phenotype and HNPPC patients without the MTS phenotype.
showed no DNA MMR protein loss. However, the tumour tissue was reported to be MSI-H.

The majority of the 27 germline mutations were located in the MSH2 gene (25/27 = 93%) and only two mutations (7%) were identified in MLH1. This proportion of MSH2 mutations was much higher than in a large sample of 105 mutation carriers with the HNPCC phenotype (without MTS). Among these 105 patients, 54 (51%) MSH2 mutations and 51 (49%) MLH1 mutations were detected (unpublished own observation). The overrepresentation of MSH2 mutations in patients with the MTS phenotype compared to HNPCC patients without the MTS phenotype is highly significant (p < 0.001; two-tailed Fisher’s exact test).

The MSH2 mutations were distributed over the whole MSH2 gene. Approximately 10% of the MSH2 mutations were large genomic deletions.

A total of 40 index patients had originally been ascertained on the basis of an MTS or a sebaceous neoplasm, only patient 62 being from a previously known HNPCC family. The personal history of all 27 mutation carriers was available, as was the family history of most of the mutation carriers. Fifteen of the 27 mutation carriers met the Bethesda criteria for HNPCC (see comments in Rodriguez-Bigas et al.).

The family history of the four patients who did not meet the Bethesda criteria would have led to a suspicion of HNPCC. Eight of the identified mutation carriers did not meet the Bethesda guidelines for HNPCC. However, classic mutational hot spots do not exist.

No specific mutations or certain MSH2 domains are correlated with the MTS phenotype. Additionally, a large proportion of the mutations detected in our MTS patients were also previously described in HNPCC patients or families without the MTS phenotype. Obviously, MSH2 mutation carriers are at a much higher risk of developing a sebaceous neoplasm compared to MLH1 mutation carriers. However, the overall incidence of the rare sebaceous neoplasms compared to other HNPCC malignancies is much lower.

The MSH2 mutations detected in our MTS sample were evenly distributed over the whole length of the gene, an observation that is also made in HNPCC patients (ICG-HNPCC mutation database and own unpublished observation). Each of the mutations occurred only once in our index patients. This finding may be due to the sample size and does not contradict the findings in large HNPCC patient samples, where some mutations were identified more than once in unrelated patients. However, classic mutational hot spots do not exist.

We performed screening for germline mutations in MSH2 and MLH1 genes in 41 unrelated index patients diagnosed with MTS or suspected of MTS, most of them pre-selected for MMR deficiency in their tumour tissue. We identified 27 germline mutations in the DNA MMR genes MSH2 and MLH1, 93% of these mutations being located in MSH2. While in MTS index patients (without the MTS phenotype) the ratio of mutations in MSH2 and MLH1 was about 1:1 (unpublished own observation and Papadopoulos and Lindblom), the proportion of MSH2 mutations was significantly higher in the MTS patients reported in this study.

Indications that MSH2 is the causative gene in most of the MTS patients have been previously described in the literature: there are several case reports or reports on small MTS patient samples presenting an MSH2 mutation. In our previously reported 11 mutation carriers, MSH2 was found to be the causative gene in nine cases. Other authors reported a total of 11 different MSH2 mutations in MTS patients. In contrast, only three different MLH1 mutations have been reported in MTS patients so far, and two of these are part of our MTS sample.

We did not examine the MSH6 gene in the 14 patients in whom no mutation in the MSH2 or MLH1 genes was detected. In 11 of these 14 patients, immunohistochemical examination of tumour tissues was performed, and loss of MSH2 or MLH1 expression was found in six and four cases, respectively. One tumour showed weak expression of both MSH2 and MLH1, although evaluation of this tumour remains questionable.

The vast majority of tumours in patients with a germline mutation in the MSH6 gene show normal MSH2 and MLH1 staining. Therefore, it is very unlikely for as many as 10 of the 14 patients to exhibit an MSH6 germline mutation.

To date, few other genotype–phenotype correlations have been reported for MSH2 mutation carriers. The lifetime risk of developing cancer at any site or in the urinary tract has been reported to be significantly higher for MSH2 mutation carriers than for MLH1 mutation carriers. According to the same study, the risk of developing cancer of the colorectum, endometrium, ovaries, stomach, and brain was also higher in MSH2 mutation carriers. However, this difference was not significant.

Literature data also point towards mutations in MSH6 resulting in a different phenotype compared to mutations in MSH2 and MLH1. A high proportion of MSH6 germline mutations were identified in atypical HNPCC families with a high frequency of atypical hyperplastic lesions and carcinomas of the endometrium. To date, no mutations in the MSH6 gene have been reported in patients with the MTS phenotype.

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The overall mutation detection rate of 66% and the detection of large genomic deletions in 7% of our MTS patients are both in line with the mutation and deletion detection rates in a large sample of HNPCC patients (61% and 10.6%, respectively) recently found by our group.

Our finding of a clear-cut genotype–phenotype correlation has consequences for mutation screening in MTS patients or HNPCC index patients with reported MTS patients among their relatives. As the chance of finding an MSH2 mutation in these patients is relatively high, mutation screening should start with the MSH2 gene, unless immunohistochemical results of the patients’ tumour tissue are available and point towards another causative DNA MMR gene. A search for large genomic deletions should be included in the mutation screening protocols for MTS patients.

The Bethesda guidelines for HNPCC list a number of tumours as specific malignancies for HNPCC. However, sebaceous neoplasms, the typical tumours of the MTS phenotype, are not mentioned as indicators for HNPCC (see comments in Rodriguez-Bigas et al.). We therefore raise the question whether our mutation carriers would have been detected by applying the Bethesda criteria as a first pre-selection step prior to tumour tissue and mutation analysis.

The evaluation of a patient for possible HNPCC by applying the Bethesda guidelines requires the patient’s personal history of all 27 mutation carriers was available, as was the family history of most of the mutation carriers. Fifteen of the 27 mutation carriers met the Bethesda criteria for HNPCC (see comments in Rodriguez-Bigas et al.).

Eight of the identified mutation carriers did not meet the Bethesda guidelines for HNPCC. In two of these eight patients, no family history was available.

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mutations were identified in selected by tumour tissue analysis. As the vast majority of malignancies listed in the Bethesda guidelines. We feel pointed out previously, the rare sebaceous neoplasms should make the diagnosis of a sebaceous neoplasm and could therefore be the first person to raise the suspicion of HNPCC. In fact, 19 of our 27 mutation carriers alone or in combination with their family history met the Bethesda criteria. Thus, these 19 patients could have been diagnosed with hereditary non-polyposis colorectal cancer: an updated review.

There are several criteria for mutation analysis in MTS patients or HNPCC index patients with reported MTS patients among their relatives. Interestingly, a remarkable proportion of the mutation carriers (more than 20%) would have been overlooked if the Bethesda criteria instead of the MTS phenotype had been applied for ascertainment.

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