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Muir-Torre Phenotype Has a Frequency of DNA Mismatch-Repair-Gene Mutations Similar to That in Hereditary Nonpolyposis Colorectal Cancer Families Defined by the Amsterdam Criteria

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Summary

Muir-Torre syndrome (MTS) is an autosomal dominant disease defined by the coincidence of at least one sebaceous skin tumor and one internal malignancy. About half of MTS patients are affected by colorectal cancer. In a subgroup of MTS patients the disease has an underlying DNA mismatch-repair (MMR) defect and thus is allelic to hereditary nonpolyposis colorectal cancer (HNPCC). The purpose of this study was to examine to what extent germ-line mutations in DNA MMR genes are the underlying cause of the MTS phenotype. We ascertained 16 MTS patients with sebaceous skin tumors and colorectal cancer, and we examined their skin and visceral tumors for microsatellite instability. All the patients exhibited high genomic instability in at least one tumor. The search for germ-line mutations in the hMSH2 and hMLH1 genes in 13 of the MTS patients revealed truncating mutations in 9 (69%): eight mutations in the hMSH2 gene and one in the hMLH1 gene. This is the first systematic search for germ-line mutations in patients ascertained on the basis of sebaceous skin tumors. Our results indicate that (1) MTS patients exhibit significantly more mutations in the hMSH2 gene than in the hMLH1 gene; and (2) the subpopulation of MTS patients who are also affected by colorectal cancer, irrespective of family history and age at onset of tumors, may have a likelihood for an underlying DNA MMR defect similar to that for patients with a family history fulfilling the strict clinical criteria for HNPCC.

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Introduction

Autosomal dominant Muir-Torre syndrome (MTS; MIM 158320) is defined by the combined occurrence of at least one sebaceous skin tumor and one internal malignancy in the same patient (for a review, see Cohen et al. 1991; Schwartz and Torre 1995). Approximately 150 patients have been reported in the literature, so far. The sebaceous skin tumors include sebaceous adenomas, epitheliomas, and carcinomas. The spectrum of internal cancers in MTS is similar to that in hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome; MIM 120435 and 120436). The most common internal malignancy is colorectal cancer, accounting for ~50% of all primary cancers in MTS. Approximately 15% of female MTS patients develop endometrial cancer (Cohen et al. 1991).

Patients with MTS also were found in families with HNPCC. Hence, it has been postulated that some cases of MTS may represent the more full phenotypic expression of HNPCC (Lynch et al. 1981). HNPCC is caused by a germ-line mutation in one of at least five DNA mismatch-repair (MMR) genes—namely, hMSH2, hMLH1, hPMS1, or hPMS2 (for a review, see Papadopoulos and Lindblom 1997; Peltomäki and Vasen 1997) or hMSH6/GTBP (Miyaki et al. 1997). This condition predisposes to genetic instability (microsatellite instability [MIN]) in tumor tissue. In HNPCC families, >150 different germ-line mutations in the five MMR genes have been reported. The large majority of these mutations are almost equally distributed among the two genes hMSH2 and hMLH1 (Liu et al. 1996; Papadopoulos and Lindblom 1997; Peltomäki and Vasen 1997; Wehner et al. 1997; Wijnen et al. 1997). So far, only weak evidence for a genotype-phenotype correlation has been found (Vasen et al. 1996; Jäger et al. 1997; Papadopoulos and Lindblom 1997).

Honchel et al. (1994) detected MIN in cutaneous and

Table 1

Clinical and Molecular Data of the Patients with Muir-Torre Syndrome

Patient	Sex	Age at Diagnosis (years)	Tumor Spectrum[a]	Site	MIN[b]	Family History (Age at Diagnosis [years])[c]	Germ-Line Mutation
122a	Female	48	Colorectal carcinoma	Cecum		Daughter (122b): sebaceous gland tumors (42–45)	Not detected
		53	Keratoacanthoma				
		53	Trichoepithelioma				
		56	Colorectal carcinoma	Transverse colon			
		61–62	Sebaceous carcinomas (multiple)	Capillitium, face, shoulder, mons pubis			
		61–65	Sebaceous hyperplasias (multiple)	Face, temple			
		62	Colonic adenomas (2 ×)	Rectum			
		61–65	Sebaceous adenomas (multiple)	Face, mons pubis			
		61–65	Sebaceous epitheliomas (multiple)	Temple, upper back			
		65	Sebaceous epithelioma	Face	+ (5/7)		
		65	Sebaceous epithelioma	Face	+ (6/6)		
122b (daughter of 122a)	Female	42	Sebaceous epithelioma	Face			
		44 and 45	Sebaceous adenomas (multiple)	Face, neck			
		44	Sebaceous adenoma	Mons pubis	+ (2/8)		
130[d]	Male	57	Colorectal carcinoma	Rectum		Amsterdam criteria;[e] brother: colorectal carcinoma (33); father: colorectal carcinoma	hMSH2, exon 2 (289ins22)
		57	Colonic adenomas (3 ×)	Descending colon			
		61	Sebaceous adenomas (multiple)	Face, chest			
		61	Sebaceous adenoma	Face	+ (4/6)		
		61	Sebaceous epitheliomas (multiple)	Face			
		61	Sebaceous epithelioma	Face	+ (4/4)		
		61	Sebaceous hyperplasias	Face, chest			
		61	Keratoacanthoma	Face	− (0/11)		
132	Male	45 to present	Sebaceous skin tumors (multiple)	Face, back, arm		Father: leukemia (84); two brothers of father: brain tumor (>80) and "cancer" (>80); mother: gastric carcinoma (47); 10 siblings of mother: "cancer"	hMSH2, exon 11 (1677delT)
		51	Colorectal carcinoma	Transverse colon			
		57	Colorectal carcinoma	Transverse colon			
		57–65	Colonic adenomas (5–6 ×)				
		65	Actinic keratosis				
		65	Sebaceous adenoma (cystic morphology)	Abdominal wall	+ (6/7)		
		65	Sebaceous adenoma	Lower back			
133	Male	40	Colorectal carcinoma	Ascending colon		Father: prostate cancer (76)	hMSH2, exon 12 (1809delT)
		45	Sebaceous adenoma (cystic morphology)	Back	+ (4/5)		

134	Male	53	Colorectal carcinoma	Sigmoid colon		Unknown	Not examined
		69	Colorectal carcinoma	Transverse colon			
		69	Sebaceous adenoma (cystic morphology)	Abdomen	+ (4/6)		
162	Male	52	Colorectal carcinoma	Ascending colon		Brother: "cancer" (33); father: prostate cancer (79)	Not detected
		65–68	Sebaceous adenomas (multiple)	Forehead, neck, upper back			
		68	Sebaceous adenoma	Face	+ (3/7)		
		68	Sebaceous adenoma	Face	+ (3/8)		
167[d]	Male	44	Seminoma	Left testicle		Mother: colorectal and endometrial carcinoma (52)	hMSH2, exon 11 (1699delAAACA)
		44	Colorectal carcinoma	Cecum			
		53	Squamous cell carcinoma of keratoacanthoma type	Upper back	+ (4/7)		
			Sebaceous lesions	Face			
199	Male	37	Sebaceous adenoma	Back		Amsterdam criteria;[e] father, grandfather, and grandfather's brothers: bowel cancer (<40)	Not detected
		40	Sebaceous epithelioma	Temple	+ (3/6)		
		40	Gastric adenoma				
		40	Colorectal adenoma	Rectum	+ (6/6)		
		40	Small bowel carcinoma	Jejunum	+ (6/6)		
		41	Colorectal carcinoma	Ileocecum	+ (4/6)		
		41	Colorectal adenomas (8 ×)				
278	Male	26	Hodgkin disease			Daughter: colorectal carcinoma (31)	hMSH2, exon 5 (862CAG→TAG)[f]
		45	Colorectal adenoma				
		54	Colorectal carcinoma	Descending colon			
		55	Sebaceous adenoma	Face	+ (3/5)		
		55	Sebaceous hyperplasias (multiple)	Face			
MTS-K1a	Female	45	Endometrial carcinoma		+ (8/9)	Daughter (MTS-K1b): colorectal (35) and endometrial carcinoma (47); first brother: brain tumor (75); second brother: hepatic cancer (70); daughter of second brother: colorectal carcinoma (35); third brother: prostate cancer (80); sister: breast cancer (35)	Not detected
		54–57	Sebaceous adenomas (multiple)	Face			
		56	Sebaceous adenoma	Face	+ (7/8)		
		57	Sebaceous epithelioma	Abdominal wall	+ (9/10)		
MTS-Klb (daughter of MTS-K1a)	Female	35	Colorectal carcinoma	Ascending colon	+ (7/7)		
		47	Endometrial carcinoma		+ (6/6)		
MTS-K2a	Male	46	Colorectal carcinoma	Transverse colon	+ (5/7)	Sister of mother (MTS-K2b): MTS; brother of mother: colorectal carcinoma (52); first daughter of mother's brother: brain glioma (36); second daughter of mother's brother: endometrial carcinoma (26)	hMSH2, exon 10 (1576delA)
		46	Sebaceous adenomas	Face			
		53	Urothelial carcinoma	Urinary bladder			
		54–57	Colorectal adenomas (multiple)				
		56	Sebaceous epithelioma	Face	+ (5/6)		
		63	Colorectal carcinoma	Ascending colon			

(*continued*)

Table 1 (continued)

Patient	Sex	Age at Diagnosis (years)	Tumor Spectrum[a]	Site	MIN[b]	Family History (Age at Diagnosis [years])[c]	Germ-Line Mutation
MTS-K2b (aunt of MTS-K2b)	Female	62	Endometrial carcinoma				hMSH2, exon 10 (1576delA)
		68	Colorectal carcinoma	Cecum			
		69	Squamous cell carcinoma	Face			
		70	Colorectal carcinoma	Rectum			
		70	Urothelial carcinoma	Ureter			
		76	Sebaceous adenoma	Forehead			
		76	Trichilemmal cysts	Capillitium, neck			
		76	Seborrhoic keratoses	Face, trunk			
MTS-K8	Male	38	Basal cell carcinoma	Face		Father: colorectal carcinoma (52); pancreatic carcinoma (57); sister of father: cancer of the spinal marrow (45); grandmother (of the patient's father): "abdominal tumor" (75)	hMSH2, exon 13 (2015delT)
		50	Keratoacanthomas (multiple)	Face, hands, trunk			
		50	Squamous cell carcinomas (multiple)	Face, hands, trunk			
		50	Sebaceous adenomas (multiple)	Upper back			
		50	Sebaceous adenoma	Abdominal wall	+ (7/9)		
		51	Colorectal carcinoma	Sigmoid colon			
		51	Colorectal carcinoma	Cecum			
MTS-K10	Male	55	Sebaceous epithelioma	Face	+ (6/9)	Negative family history	hMSH2, exon 3 (380delAT)
		55	Sebaceous epithelioma	Leg	+ (2/6)		
		55	Sebaceous epithelioma	Capillitium	+ (7/10)		
		56	Prostate cancer				
		57	Colorectal carcinoma	Descending colon			
MTS-K14	Male	42	Leiomyosarcoma of the skin	Shoulder		Unknown	hMLH1, exon 16 (1884delGGAAA)
		46	Colorectal carcinoma	Cecum			
		47	Colorectal carcinoma	Transverse colon			
		52	Sebaceous epithelioma	Forehead	+ (5/10)		
		52	Sebaceous hyperplasia	Forehead			
MTS-K17	Male	<61	Colorectal carcinoma			Unknown	Not examined
			Skin tumors (multiple)	Face			
		61	Sebaceous epithelioma	Neck	+ (8/9)		
T-12	Female	<81	Colorectal carcinomas (2 ×)			Unknown	Not examined
		81	Sebaceous tumor	Chest	+ (3/6)		

[a] Tumors examined for MIN are underlined.
[b] No. of unstable markers/no. of markers examined.
[c] Quotation marks indicate that no detailed information was available for the type of tumor or cancer, for that family member.
[d] Previously described by Kruse et al. (1996).
[e] Amsterdam criteria (Vasen et al. 1991): (1) colorectal cancer in at least three family members; (2) one family member must be a first-degree relative of the other two; and (3) the diagnosis must have been established in at least one relative <50 years of age.
[f] The same mutation also has been identified in an HNPCC family studied by Wijnen et al. (1995).

internal tumor tissues from 6 of 13 MTS patients. Consequently, they suggested that MTS consists of two subgroups, one of which is allelic to HNPCC. However, these patients were not examined for germ-line mutations in MMR genes. With regard to MTS families, only seven germ-line mutations in MMR genes have been published, all but one of which affect the hMSH2 gene (Hall et al. 1994; Kolodner et al. 1994; Liu et al. 1994; Bapat et al. 1996; Kruse et al. 1996; Esche et al. 1997).

The purpose of this study was to examine to what extent germ-line mutations in DNA MMR genes are the underlying cause of the MTS phenotype. We therefore extended our previous molecular genetic examination of 2 MTS patients (Kruse et al. 1996) and examined 14 additional MTS patients, for MMR defects. The patients had been ascertained on the basis of sebaceous skin tumors and colorectal cancer, irrespective of family history and age at onset of tumors.

Patients and Methods

Patient Selection

A total of 16 patients with the clinical diagnosis of MTS were ascertained on the basis of sebaceous skin tumors and colorectal or endometrial cancer. Thirteen of them were referred to us by dermatologists or pathologists, and 3 were known from previous case reports (Bisceglia and Zenarola 1991; Panday et al. 1993; Hartig et al. 1995). Tumor tissue and blood samples, as well as clinical data, were obtained with appropriate informed consent from the patients.

Isolation of Genomic DNA and RNA from Blood Samples

Genomic DNA was isolated from peripheral blood (Miller et al. 1988). To isolate RNA, white blood cells were obtained from 10 ml of EDTA-anticoagulated blood (within 24 h after sampling) by use of Ficoll (Pharmacia Biotech), and RNA was extracted by use of the Trizol reagent (Gibco BRL), in accordance with the manufacturer's instructions.

Assessment of MIN

Tumor DNA was extracted from microdissected paraffin-embedded tumor tissue by use of the QIAamp tissue kit (QIAGEN). If no blood sample was available, surrounding normal tissue was used to extract normal DNA. Paired normal and tumor DNA were analyzed for MIN with $\leqslant 11$ microsatellite markers—namely, two poly-A repeats (BAT25 and BAT26) and nine dinucleotide repeats (D2S123, D2S136, D3S1298, D5S346, D6S470, D16S663, D18S35, D18S37, and D21S171). The MIN phenotype is detected as an allelic mobility shift during electrophoretic runs on denaturing gels. A tumor was defined to exhibit MIN (MIN^+) if additional alleles were observed with at least two markers.

Search for Germ-Line Mutations

SSCP analysis and heteroduplex analysis (HD).—All the exons of the hMLH1 and hMSH2 genes were amplified by PCR, by use of the primers described by Kolodner et al. (1994, 1995). PCR products were examined by SSCP analysis and HD and were visualized by silver staining, as described elsewhere (Friedl et al. 1993).

Protein truncation test (PTT).—An RNA aliquot was reverse transcribed with M-MLV reverse transcriptase and an oligo-dT primer (Gibco BRL). For PCR amplification, both hMSH2 and hMLH1 cDNA were amplified in two overlapping segments of 1.2–1.7 kb and were transcribed and translated in vitro by use of the TNT-T7 Quick coupled transcription/translation system (Promega) and ^{35}S-methionin, as described elsewhere (Luce et al. 1995).

Direct sequencing.—Paired biotinylated and M13-tailed primers for the hMSH2 and hMLH1 genes (Kolodner et al. 1994, 1995) were used to amplify genomic DNA sequences. Single-strand DNA obtained with Dynabeads (Dynal) was sequenced with Sequenase 2.0 (Amersham) by use of M13 universal sequencing primer. Mutations were confirmed by repetition of both the amplification and the sequencing steps.

Results

Paraffin-embedded tumor tissues were obtained from 16 unrelated patients with MTS and from two affected relatives. Fifteen of the index patients had developed at least one colorectal malignancy. The only MTS patient without colorectal cancer had an endometrial cancer, whereas her daughter had developed a colorectal cancer (table 1(). In four MTS patients (132, 199, MTS-K8, and MTS-K10), skin tumors had developed before the visceral malignancy. One of these patients does not have a relative with cancer. Two patients have a family history of visceral cancer but do not fulfill the strict Amsterdam criteria for HNPCC (Vasen et al. 1991). In one MTS patient (MTS-K2a), the skin and colorectal tumors developed synchronously. In the remaining 11 MTS patients, at least one visceral neoplasm was diagnosed before the manifestation of the characteristic skin lesions.

Twenty-four skin tumors and 7 visceral tumors, from 16 MTS patients, were examined for MIN as the characteristic molecular feature of an MMR defect. At least 1 skin tumor from each patient exhibited MIN, as detected by a minimum of three microsatellite markers (fig. 1 and table 1). All but 1 of all examined tumors were MIN^+. Twenty of the 23 MIN^+ skin tumors and all 7 internal tumors showed high instability, with >40% of the examined markers being unstable (table 1).

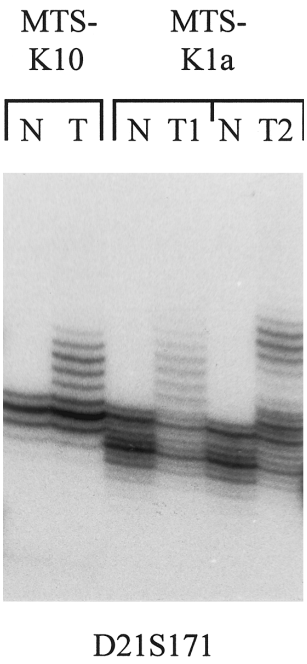

Figure 1 MIN in patients MTS-K10 and MTS-K1a. DNA from peripheral blood (lanes N) and skin tumor tissues (lane T, sebaceous epithelioma; lane T1, sebaceous adenoma; and lane T2, sebaceous epithelioma) was examined by use of microsatellite marker D21S171 and was visualized by autoradiography after separation on a denaturing gel.

Thirteen patients were examined for germ-line mutations in the two MMR genes hMSH2 and hMLH1 (table 1). Of the remaining 3 patients, sufficient normal DNA or RNA was not available for mutation analysis.

In 6 of the 13 patients, mRNA was available, and a PTT was performed first. In 3 of these patients, truncated proteins were observed in the hMSH2 gene. In the remaining 10 patients, we screened the entire coding regions and the exon/intron boundaries of the two genes, by use of both SSCP analysis and HD. Aberrant patterns were obtained from an additional 6 patients.

Sequencing revealed eight germ-line mutations (seven frameshift and one nonsense) in the hMSH2 gene and one frameshift mutation in the hMLH1 gene (table 1). All but one of the mutations are unique to our patient sample. The hMSH2 mutations identified in our MTS patient sample were distributed over the entire gene (table 1).

Discussion

We systematically examined 16 MTS patients affected by cancer of the colorectum or endometrium, for MMR defects. The patients were ascertained on the basis of their characteristic skin lesions, irrespective of family history or early onset of colorectal cancer. In each of these patients, at least one sebaceous skin tumor exhibited MIN, as detected by a minimum of 40% of the markers tested, thus fulfilling the criteria for MIN proposed by Bocker et al. (1997). These results are in accordance with the study by Honchel et al. (1994), who also found a high instability in sebaceous skin tumors of MTS patients affected by colorectal cancer.

We used DNA-based and mRNA-based methods to screen 13 MTS patients for underlying germ-line mutations in the MMR genes hMSH2 and hMLH1 and identified nine mutations (eight in the hMSH2 gene and only one in the hMLH1 gene) that are predicted to lead to a truncated protein. This finding supports the previously observed predominance of hMSH2 mutations in MTS. It contrasts with the mutation spectrum in patients with "pure" HNPCC: in the International Collaborative Group–HNPCC database, 42 mutations in the hMSH2 gene and 75 in the hMLH1 gene were reported (Peltomäki and Vasen 1997). Another peculiarity was the preponderance of males with MTS (13 males vs. 3 females, among the index patients; see table 1), which is in accordance with previous observations (Schwartz and Torre 1995).

In 41% of all MTS cases reported so far, the sebaceous skin tumors preceded or occurred concurrently with the internal malignancy (Schwartz and Torre 1995). In this study, skin tumors in 4 (25%) of the 16 MTS patients were diagnosed earlier than the internal neoplasm, and the skin and internal tumors in 1 patient were diagnosed concurrently. For the remaining 11 MTS patients, the tentative diagnosis of a cancer-predisposition syndrome was based on dermatological examination and not on internal tumors or family history. Thus, in a high proportion of patients, skin tumors characteristic of MTS can serve as premonitory physical stigmata for an underlying cancer predisposition.

A variety of sebaceous skin tumors observed in MTS patients are distinctive but difficult to classify (Burgdorf et al. 1986). This is especially true for some large cystic and nodular lesions, also observed in our patients (table 1), which seem to be marker lesions because, so far, they have been seen only in patients with MTS.

The unique clinical feature of 15 of our MTS patients was the occurrence of at least one colorectal carcinoma. In the study by Honchel et al. (1994), 6 of 9 MTS patients with colorectal carcinoma and none of the 4 MTS patients without colorectal carcinoma exhibited MIN. Considered together, their results and the results of this study allow the definition of a distinct phenotype predicted to be MMR defective—that is, a patient with a skin tumor characteristic of MTS and with a colorectal carcinoma. This phenotype seems to have the same power to predict an MMR defect as the Amsterdam criteria (Vasen et al. 1991). In 9 (69%) of 13 MTS patients, we detected germ-line mutations in either the

hMSH2 or the hMLH1 genes, whereas an extensive mutation analysis of HNPCC kindreds revealed a mutation in these two genes in 31 (64%) of 48 families (Liu et al. 1996). In conclusion, we present the first systematic screening for MMR-gene germ-line mutations in MTS patients. Despite our limited sample size, we postulate that the mutation-detection rate in the subpopulation of MTS patients who exhibit a colorectal carcinoma may be similar to that for HNPCC patients ascertained by family history, age at onset, and MIN (Liu et al. 1996).

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

International Collaborative Group–HNPCC database, http://www.nfdht.nl

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for MTS [MIM 158320] and HNPCC/Lynch syndrome [MIM 120435 and 120436])

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