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Acknowledgements—This work was supported by grants from the Swedish Cancer Society. The following members of the South-East Sweden Breast Cancer Group are gratefully acknowledged: L.-G. Arnesson, B. Boeryd, T. Hatschek, M. Sundén (Linköping), H. Bång (Motala), E. Einarsson (Eksjö-Nässjö), C. Grant, A.-C. Källström, S. Norrby (Norrköping), R. Gustavsson, S. Lundberg, B. Norberg (Jönköping), A. Henning (Oskarshamn), L. Mellblom, Å. Molde (Kalmar), A. Stubberöd (Värnamo), V. Störgren Fordell (Finspång) and G. Tejler (Västervik).

Pergamon

European Journal of Cancer Vol. 30A, No. 2, pp. 180–182, 1994
Elsevier Science Ltd. Printed in Great Britain
0959–8049/94 $6.00 + 0.00

0959-8049(93)E0072-X

Genetic Linkage in Muir-Torre Syndrome to the Same Chromosomal Region as Cancer Family Syndrome

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The Muir-Torre syndrome, in which sebaceous gland tumours occur in association with internal malignancy, is inherited as an autosomal dominant disorder. Many features of the syndrome are similar to those of the Lynch II cancer family syndrome, and thus the two disorders might share a common genetic basis. We typed two large families with DNA markers on chromosome 2p around D2S123, a site recently shown to be linked to the Lynch II syndrome. LOD scores at this locus demonstrated significant and tight linkage to D2S123, suggesting that defects in the same gene might give rise to both syndromes.

Eur J Cancer, Vol. 30A, No. 2, pp. 180–182, 1994

INTRODUCTION

MUIR-TORRE syndrome is a genodermatosis (McKusick number 158320) [1] characterised by the presence of sebaceous gland tumours (adenoma, epithelioma or carcinoma) associated with one or more of a wide variety of internal malignancies, particularly colorectal, endometrial, urological and upper gastrointestinal tumours, as well as other skin tumours, notably keratoacanthomas and basal cell carcinomas [2]. Affected members have a high incidence of synchronous and metachronous tumours yet, despite this, survival is frequently prolonged [1]. Many cases show a strong family history consistent with autosomal dominant inheritance, and it has been proposed that the syndrome is an unusual phenotypic variant of the Lynch II cancer family syndrome [3], also known as hereditary non-polyposis colorectal cancer. Following the recent report of genetic linkage to the D2S123 locus on chromosome 2p for the Lynch II syndrome [4], we wished to see if the Muir-Torre syndrome gene also mapped to the same locus, thus testing the hypothesis that both syndromes share a common genetic basis.

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Received 15 Dec. 1993; accepted 16 Dec. 1993.

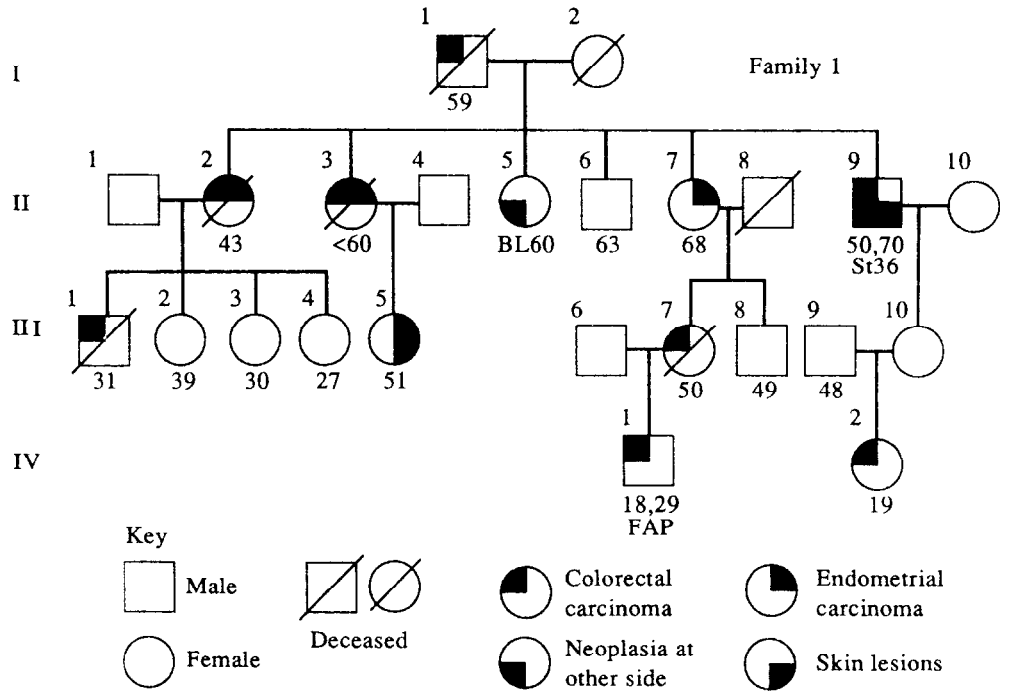

Fig. 1. Pedigree of Family 1 showing tumour details. Symbols and shading are as shown in the key. Skin lesions include sebaceous adenoma, epithelioma and hyperplasia, basal cell carcinoma and keratoacanthoma. Family members are identified by their generation (roman numeral) and number (arabic numeral), with the numbers beneath the symbols indicating the age of colorectal or endometrial cancer diagnosis or, if unaffected, current age or age at death. For other conditions, the site and age of diagnosis are also indicated. Abbreviations are for adenocarcinomas of the cervix (Cx), ovary (Ov), small bowel (SB) and stomach (St);transitional cell carcinoma of bladder (BL) and ureter (Ur); carcinoma of the nasal septum (NS); chronic lymphatic leukaemia (CLL); sarcoma of bone (Sa); rectal polyps (Po); familial adenomatous polyposis (FAP).

SUBJECTS AND METHODS

Two extended families were chosen for analysis (Figs 1, 2), with family members showing the classical features of the Muir-Torre syndrome. Typical skin tumours developed in one member of Family 1 (II-9) and two members of Family 2 (IV-9 and IV-12); these individuals thus display the full Muir-Torre phenotype. Segregation is consistent with autosomal dominant inheritance with a high penetrance. Family 1 shows an unusual feature in that IV-1 is mentally retarded and has familial adenomatous polyposis (FAP). Cytogenetic studies and analysis of chromosome 5q markers have shown that this male has a 5q22-q23.2 deletion in his paternally-derived chromosome: this region contains the APC gene, defects in which give rise to FAP [5]. His father has no cytogenetic abnormality. IV-1 developed

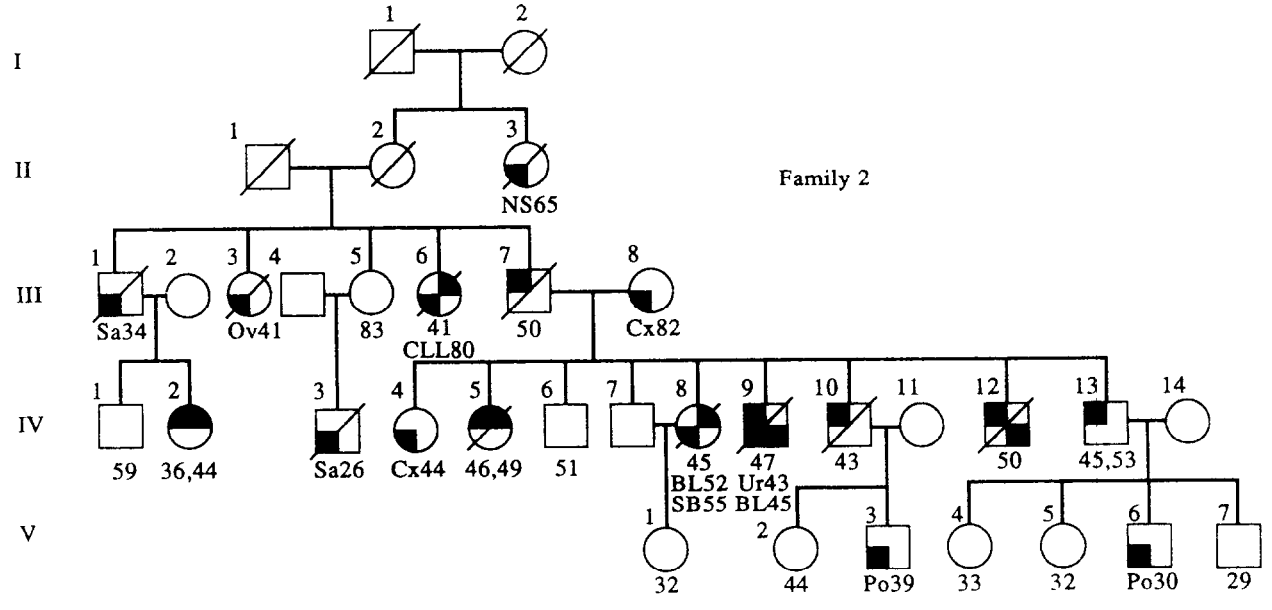

Fig. 2. Pedigree of Family 2 showing tumour details. Symbols and abbreviations as for Fig. 1.

Table 1. The LOD scores by family for D2S123 by model (L=low stringency model, H=high stringency model, see text for definitions)

Family	Model	Recombination fraction						
		0.0	0.01	0.05	0.1	0.2	0.3	0.4
1	L	1.22	1.25	1.28	1.22	0.96	0.58	0.20
2	L	2.81	2.76	2.55	2.28	1.71	1.10	0.44
Total	L	4.03	4.01	3.83	3.51	2.67	1.68	0.64
1	H	2.46	2.41	2.23	1.99	1.46	0.88	0.30
2	H	2.35	2.30	2.12	1.88	1.37	0.82	0.28
Total	H	4.81	4.72	4.35	3.87	2.83	1.70	0.59

carcinoma of the ascending colon at 18 years of age and, after colectomy, a second cancer in the rectal remnant arose when he was only 29.

Six highly polymorphic microsatellite DNA markers were typed in family members using the polymerase chain reaction (PCR). The markers were (from distal to proximal) D2S177, D2S119, D2S123, D2S147, D2S136, D2S134 [6]. Reactions were performed in a final volume of 20 μl containing approximately 50 ng genomic DNA, 50 pmol each primer, PCR buffer containing 1.5 mmol/l $MgCl_2$, 200 μmol/l dCTP, dGTP and dTTP, 5 μmol/l dATP, 1 μCi α-[^{33}P]dATP, and 1.5 U Taq polymerase. Twenty-seven cycles of 94°C for 30 s, 55°C for 75 s, 72°C for 15 s, were performed with a final extension step of 72°C for 6 min. PCR products were separated by electrophoresis on a 6.6% denaturing polyacrylamide gel, which was then fixed in 10% methanol and exposed to X-ray film.

Linkage analysis was performed using the LINKAGE package [7], making the same assumptions concerning modes of inheritance as in the original report of 2p linkage (Peltomäki, University of Helsinki): the analyses were performed twice, first, under a 'high stringency' model, which assumes that only individuals with colorectal and endometrial cancers are designated as affected, while the second (the 'low stringency' model) assumes that these individuals and, in addition, those with colorectal adenomas or single cancers at other sites are counted as affected. We designated as 'unaffected' two women with cervical cancer, two men who had screen-detected polyps before the age of 40 years (because we could not confirm that the polyps were adenomas), and IV-1 in Family 1 because a deletion of the APC locus could be sufficient to explain the early onset of colorectal cancer.

RESULTS

The LOD scores for linkage are given in Table 1 for D2S123. LOD scores for other markers in the region were 2.07 at recombination fraction (θ) = 0.05 for D2S119, and 1.33 at θ = 0.2 for D2S177, while D2S147, D2S136 and D2S134 showed no evidence in favour of linkage. Under both models, the markers (especially D2S123) show evidence in favour of linkage in each family and the summed results are strongly supportive of linkage. As previously reported [4], these results suggest that the linkage to D2S123 is tight, with no obvious recombination event between the disease locus and D2S123.

DISCUSSION

Our findings are the first to demonstrate linkage in the Muir-Torre syndrome to a locus on chromosome 2p. The similarity of features of the syndrome to the Lynch II cancer family syndrome and the linkage of both syndromes to the same region of chromosome 2 strongly suggest that the same gene is important in both conditions. This finding is analogous to the demonstration that Gardner syndrome, another genodermatosis, and FAP are both caused by mutations in the APC gene [8]. The differential expression of the phenotype must be the result of allelic variation or other genetic and/or environmental modifying influences.

A candidate gene for the Lynch II cancer family syndrome, hMSH2, has just been described [9]. This gene maps to chromosome 2p in the region of D2S123 ([9] and Dr R D Kolodner, Dana-Farber Cancer Institute, D.T.B. and N.R.H.); a mutation has been demonstrated in two affected members of Family 1 (II-9, IV-2) that is absent in two unaffected individuals (II-6, III-8) [9]. Further work on these families is in progress to investigate the role of hMSH2 in hereditary susceptibility to cancer.

Interestingly, if linkage to D2S123 is indeed tight, then the individual who has the deletion of the APC gene region on his paternally-derived chromosome should also carry a mutated copy of Lynch II gene, since he has the same 2p haplotype as other affected members in Family 1. The occurrence of two colorectal cancers by the age of 29 years is atypical even among polyposis patients [10], and may be further evidence supporting the coincidence of both susceptibilities in this individual.

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Acknowledgements—This work was supported by the Imperial Cancer Research Fund. The authors would like to thank Dr Nigel Spurr and Dr Richard Kolodner for their contribution to this research.