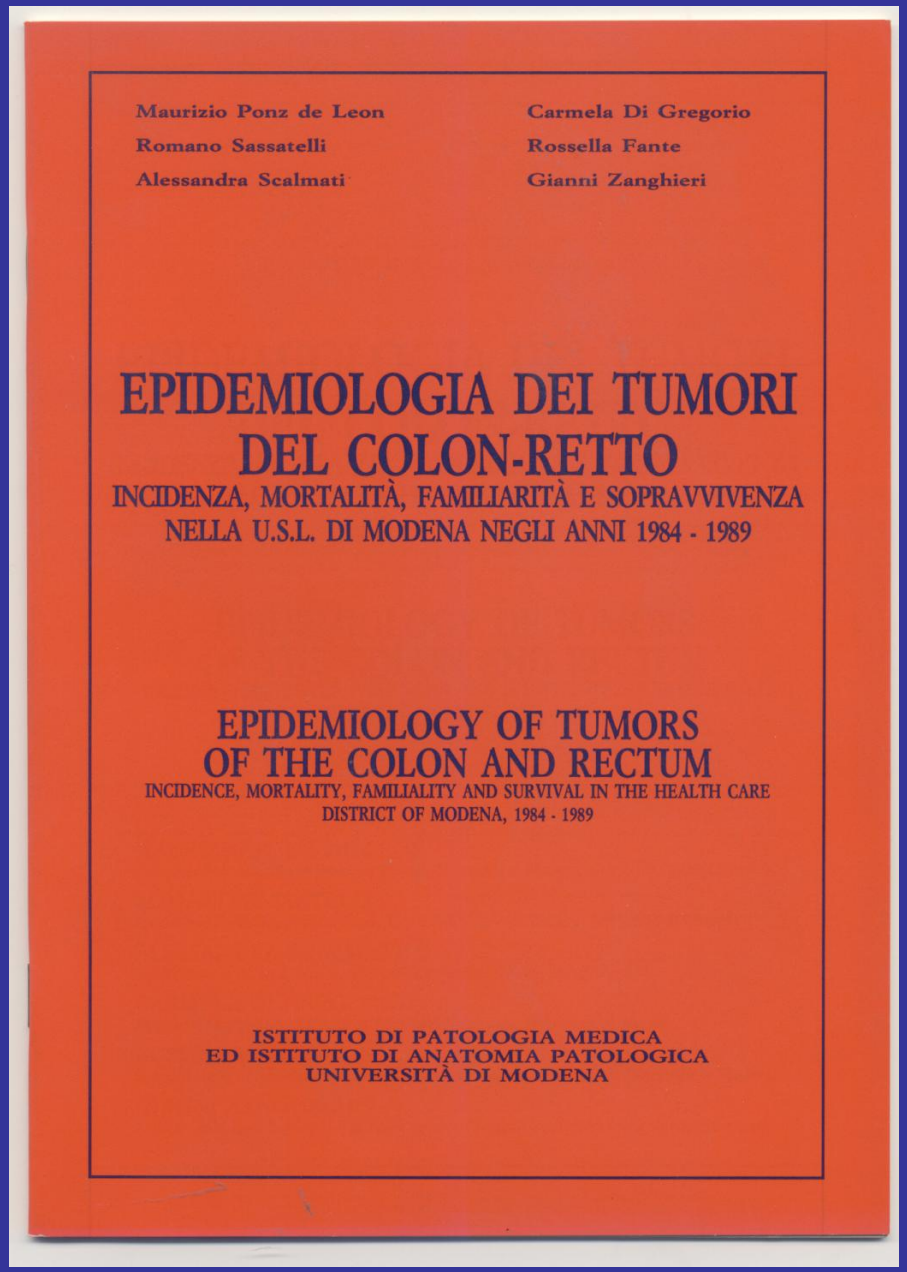
Il cancro colorettale ereditario non su poliposi: l'esperienza modenese

Piero Benatti
Dipartimento di Medicine e Specialità Mediche
Università di Modena e Reggio Emilia

Modena, 19/12/2007


Maurizio Ponz de Leon
Romano Sassatelli
Alessandra Scalmati
Carmela Di Gregorio
Rossella Fante
Gianni Zanghieri
EPIDEMIOLOGIA DEI TUMORI DEL COLON-RETTO
INCIDENZA, MORTALITÀ, FAMILIARITÀ E SOPRAVVIVENZA NELLA U.S.L. DI MODENA NEGLI ANNI 1984 - 1989
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ED ISTITUTO DI ANATOMIA PATOLOGICA
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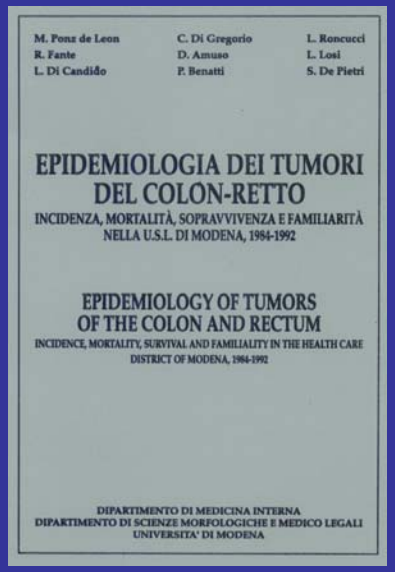
M. Ponz de Leon
R. Fante
L. Di Candido
C. Di Gregorio
D. Amuso
P. Benatti
L. Roncucci
L. Losi
S. De Pietri
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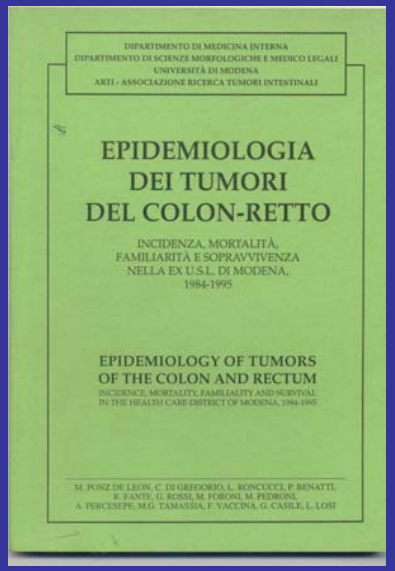
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DIPARTIMENTO DI SCIENZE MORFOLOGICHE E MEDICO LEGALI
UNIVERSITÀ DI MODENA
ARTI - ASSOCIAZIONE RICERCA TUMORI INTESTINALI
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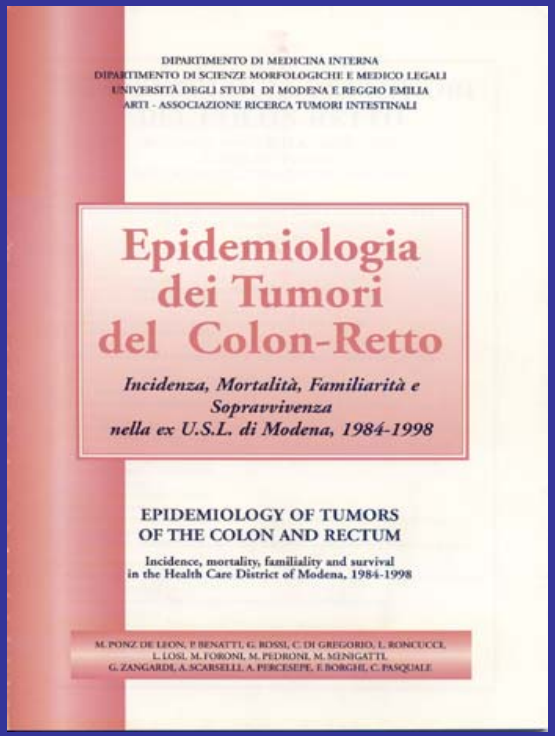
M. PONZ DE LEON, C. DI GREGORIO, L. RONCUCCI, P. BENATTI, R. FANTE, G. ROSSI, M. FORONI, M. PEDRONI, A. PERCESEPE, M.G. TAMASSIA, F. VACCINA, G. CASILE, L. LOSI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UNIVERSITÀ DEGLI STUDI DI MODENA E REGGIO EMILIA
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Epidemiologia dei Tumori del Colon-Retto
Incidenza, Mortalità, Familiarità e Sopravvivenza nella ex U.S.L. di Modena, 1984-1998
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Incidence, mortality, familiality and survival in the Health Care District of Modena, 1984-1998
M. PONZ DE LEON, P. BENATTI, G. ROSSI, C. DI GREGORIO, L. RONCUCCI, L. LOSI, M. FORONI, M. PEDRONI, M. MENIGATTI, G. ZANGARDI, A. SCARSELLI, A. PERCESEPE, F. BORGHI, C. PASQUALE

SCHEDA REGISTRO GROSSO INTESTINO – USL N° 16

Anno ..... Scheda N° .....

DATI ANAGRAFICI

Cognome ..... Nome ..... nato a ..... il .....

Domicilio (Via/Piazza n°): ..... Comune: ..... tel. .....

Professione attuale (precedente): ..... Medico curante: .....

Persona di riferimento (grado di parentela): .....

Data decesso: |_|_|_|_|_|_| Vivente al: |_|_|_|_|_|_|

DATI ANAMNESTICI

Tipo di sintomo/i ed epoca di comparsa: .....

Patologie pregresse e concomitanti: .....

.....

Fumo: ..... Alcool: ..... Farmaci: .....

NOTIZIE SUI FAMILIARI DI 1° GRADO

Cognome e Nome Grado di Parentela	Data di Nascita	Data del decesso	Causa del decesso	Luogo e data di diagnosi di patologia neoplastica

ALBERO NUCLEARE

Ricovero del: ..... Dimissioni del: .....

Reparto di degenza: ..... Data diagnosi: .....

Note: .....

.....

.....

.....

SEDE DELLA NEOPLASIA/E: .....

ADENOMI: ☐ Si ☐ No

Dukes: ..... TNM: ..... Metastasi: .....

REFERTO RADIOLOGICO (Data: |_|_|_|_|_|_|):

.....

.....

.....

REFERTO ENDOSCOPICO (Data: |_|_|_|_|_|_|):

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INTERVENTO CHIRURGICO (Data: |_|_|_|_|_|_|):

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REFERTO ISTOPATOLOGICO (N° ..... del |_|_|_|_|_|_|):

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AMSTERDAM CRITERIA

- Presenza di cancro colorettale istologicamente verificato insorto in almeno 3 membri familiari in cui almeno uno sia parente di I grado degli altri due
- Almeno due generazioni successive devono essere affette
- Almeno un caso deve essere diagnosticato prima dei 50 anni
- La Poliposi Familiare deve essere esclusa

(Dis Colon Rectum 1991)

Reprinted from CANCER, Vol. 71, No. 11, June 1, 1993
Published by J. B. Lippincott Company Printed in U.S.A.

Identification of Hereditary Nonpolyposis Colorectal Cancer in the General Population

The 6-Year Experience of a Population-Based Registry

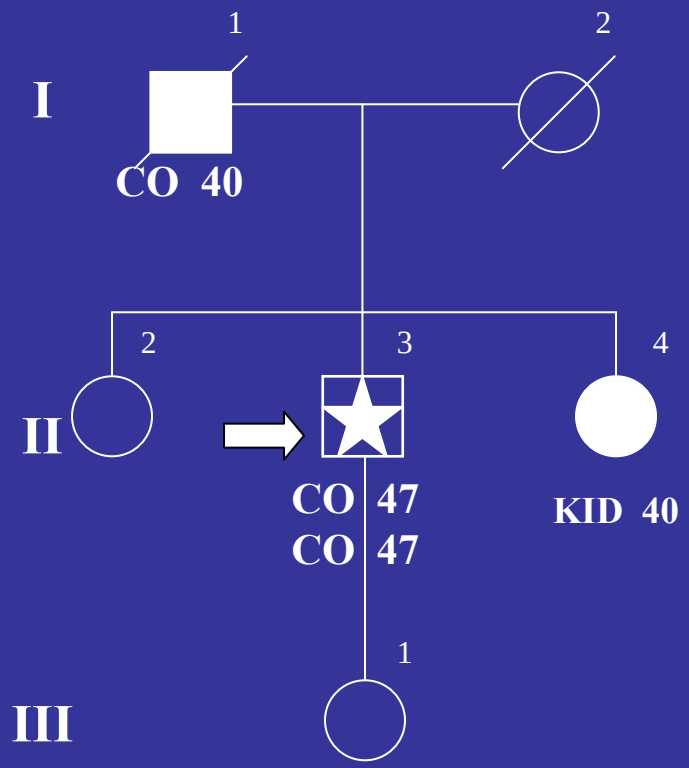
Maurizio Ponz de Leon, M.D., Romano Sassatelli, M.D., Piero Benatti, M.D.,† and Luca Roncucci, M.D.*

Background. Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) is an autosomal dominant disease characterized by early-onset intestinal neoplasms, localization of tumors in the proximal colon, and frequent association with cancers at other sites, especially the endometrium, skin, and stomach. The identification of HNPCC is often difficult, owing to the lack of biomarkers and the extreme frequency of sporadic colorectal cancer in the Western World.

Methods. The authors reviewed the clinical data and the family trees of all patients (n = 817) with colorectal malignancies registered in the local health district be- of total), three criteria (58 families, 7%), two criteria (73, 8.9%), or less than two criteria (203 families, 24.8%). The remaining 380 case families did not show criteria suggesting a genetic component. One hundred thirty-three genealogic trees were extended further to gather information on second-degree and third-degree relatives. The expanded pedigrees were further analyzed to ascertain if they met the recently proposed requisites for HNPCC. Nineteen of 37 (51%) families with four criteria met the minimum requisites and could therefore be considered HNPCC. Similarly, HNPCC was diagnosed in six extended pedigrees of the three-criteria (16.6%) and in three

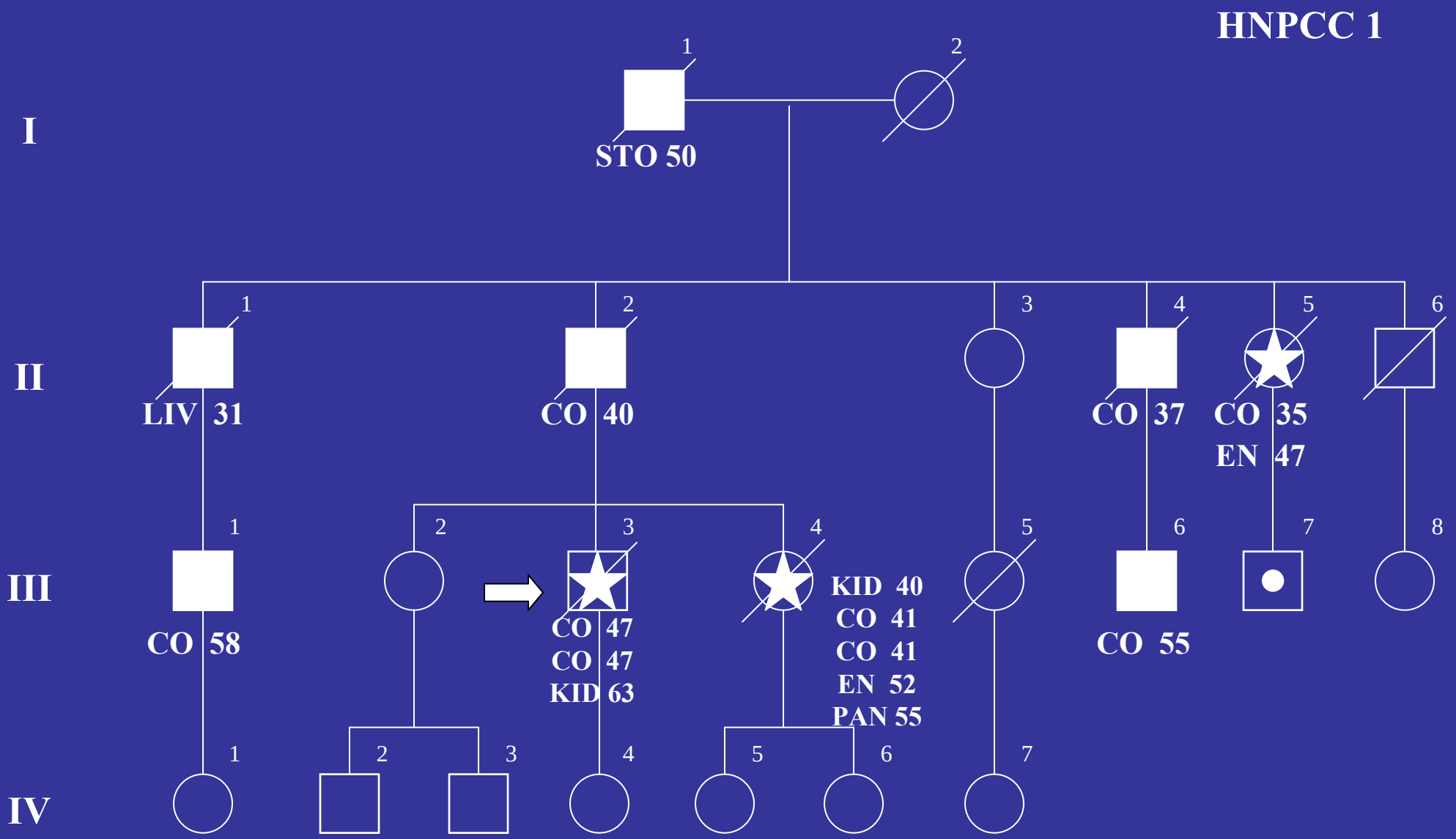
Criteri di Modena

Verticalità:	Neoplasie caratteristiche della sindrome, o in qualsiasi sede se insorte in età inferiore ai 50 anni, nei genitori o nei figli del probando.
Aggregazione:	Almeno il 50% dei soggetti in una fratria affetti da cancro in qualsiasi sede ed a qualsiasi età.
Insorgenza precoce:	Casi di neoplasia in qualsiasi sede insorti ad età inferiore ai 50 anni.
Localizzazione destra:	Neoplasie intestinali, nel probando o nei familiari di I grado, localizzate nel tratto prossimale (dal ceco alla flessura splenica).
Istotipo mucinoso:	Cancro colorettale, nel probando o nei familiari di I grado, che mostri componente mucinosa nel 50% delle cellule.
Tumori multipli:	Tumori multipli, sincroni e\o metacroni, di qualsiasi sede insorti nel probando o nei familiari di I grado.



4 criteri

Aggregazione
Verticalità
Insorgenza Precoce
Tumori multipli


HNPCC 1
I
II
III
IV
1
2
STO 50
1
2
3
4
5
6
LIV 31
CO 40
CO 37
CO 35
EN 47
1
2
3
4
5
6
7
8
CO 58
CO 47
CO 47
KID 63
KID 40
CO 41
CO 41
EN 52
PAN 55
CO 55
1
2
3
4
5
6
7

Epidemiology of HNPCC:Frequency

Study	Evaluation Clinical
Mecklin (1987)	3.8-5.0%
Kee (1991)	1.0%
Stephenson (1991)	4.0%
Westlake	3.4%
Ponz de Leon (1993)	2.6-4.5%

expressed as percent of all colorectal malignancies

L'Instabilità dei Microsatelliti (MSI)

Thibodeau, S. N.; Bren, G.; Schaid, D. :
Microsatellite instability in cancer of the proximal colon.
Lancet 260: 816-819, 1993.

[CANCER RESEARCH 53, 5849–5852, December 15, 1993]

Advances in Brief

Genomic Instability in Colorectal Cancer: Relationship to Clinicopathological Variables and Family History[1]

Ragnhild A. Lothe,[2] Päivi Peltomäki, Gunn Iren Meling, Lauri A. Aaltonen, Minna Nyström-Lahti, Lea Pylkkänen, Ketil Heimdal, Tone I. Andersen, Pål Møller, Torleiv O. Rognum, Sophie D. Fosså, Tor Haldorsen, Frøydis Langmark, Anton Brøgger, Albert de la Chapelle, and Anne-Lise Børresen

Department of Genetics, Institute for Cancer Research [R. A. L., K. H., T. I. A., P. M., A. B., A-L. B.], and Department of Medical Oncology and Radiotherapy [S. D. F.], The Norwegian Radium Hospital, 0310 Oslo, Norway; Department of Medical Genetics, P. O. Box 21, University of Helsinki, SF-00014 Helsinki, Finland [P. P., L. A. A., M. N-L., L. P., A. d. l. C.]; Institute of Forensic Medicine, The National Hospital, University of Oslo, 0027 Oslo, Norway [G. I. M., T. O. R.]; Surgical Department, Norwegian Lutheran Hospital, 0319 Oslo, Norway [G. I. M.]; Section of Medical Statistics, University of Oslo, 0317 Oslo, Norway [T. H.]; and the Norwegian Cancer Registry, Fritjof Nansens v.17, Oslo, Norway [F. L.]

Abstract

Recent reports have suggested that one or more genes may cause replication errors (RER) during colorectal tumorigenesis. Additional alleles are seen in the tumors when analyzing random microsatellite loci. We have studied seven dinucleotide repeat loci, located on seven different chromosomes, by use of polymerase chain reaction amplification and denaturing polyacrylamide gel electrophoresis. We found that 16.5% (40 of 243) colorectal cancers showed RER at one or several loci (RER+). This includes 31% (4 of 13) among cases with a strong positive family history according to previously published criteria and 17% (35 of 207) among cases with no history of familial cancer. Interestingly, no significant associ

rosatellite loci was observed as additional new alleles in tumor DNA as compared to constitutional DNA (5). Therefore, it was suggested that this gene, now called *COCA1* (colon cancer 1), might maintain replication accuracy. This implies that a mutation in such a gene could cause RER throughout the genome.

In the current study, we have determined the frequency of RER+ colorectal cancers in a large series of tumors and investigated the relationship of this phenomenon to positive family history of cancer and specific clinicopathological variables. Finally, we have addressed the possibility that microsatellite instability is a specific or general phenomenon by studying breast and testicular cancers.

Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis

Yurij Ionov*, Miguel A. Peinado*†, Sergei Malkhosyan*, Darryl Shibata‡ & Manuel Perucho*§

* California Institute of Biological Research, 11099 North Torrey Pines Road, La Jolla, California 92037, USA
‡ Department of Pathology, University of Southern California School of Medicine, Los Angeles, California 90033, USA

SPONTANEOUS errors in DNA replication have been suggested to play a significant role in neoplastic transformation and to explain the chromosomal alterations seen in cancer cells[1]. A defective replication factor could increase the mutation rate in clonal variants arising during tumour progression, but despite intensive efforts, increases in tumour cell mutation rates have not been unambiguously shown[2]. Here we use an unbiased genomic fingerprinting technique[3] to show that 12 per cent of colorectal carcinomas carry somatic deletions in poly(dA · dT) sequences and other simple repeats. We estimate that cells from these tumours can carry more than 100,000 such mutations. Only tumours with affected poly(dA · dT) sequences carry mutations in the other simple repeats examined, and such mutations can be found in all neoplastic regions of multiple tumours from the same patient, including adenomas. Tumours with these mutations show distinctive genotypic and phenotypic features. We conclude that these mutations reflect a previously undescribed form of carcinogenesis in the colon (predisposition to which may be inherited) mediated by a mutation in a DNA replication factor resulting in reduced fidelity for replication or repair (a 'mutator mutation').

The arbitrarily primed polymerase chain reaction (AP-PCR) is a PCR-based DNA fingerprinting technique using primers whose nucleotide sequence is arbitrarily chosen[3,4]. Competition between the annealing events during the initial low-stringency cycles results in the reproducible and quantitative amplification of many discrete bands during the subsequent high-stringency cycles. The genomic fingerprint obtained in a simple experiment can identify somatic genetic alterations. AP-PCR is useful for the detection and isolation of tumour-specific allelic losses and gains, thus providing a molecular alternative to cancer cytogenetics[5]. Figure 1 shows the AP-PCR fingerprints obtained with several arbitrary primers of normal and tumour tissue DNAs from two colorectal cancer patients. The differences in band mobility shown by arrows were suggestive of somatic mutations because they were tumour-tissue-specific. This phenomenon was observed with 6 of 10 unrelated primers. Without exception, there was a reduction in band size in tumour tissue. Cloning and sequencing showed that bands with altered mobilities contained repeated Alu sequences, which had undergone deletions in their poly(A) tails (data not shown). These deletions also occurred in runs of dA · dT base pairs present in DNA sequences without Alu repeats. The 550-nucleotide (nt) band amplified with primers B and C (APΔ3) is an example (Fig. 2). Comparative sequencing and PCR analyses of APΔ3 genomic and cloned sequences after AP-PCR amplification, established that the sequences predominantly present in normal and tumour tissues of patient 197 contained 18 and 14 deoxyadenosines, respectively (data not shown). Therefore, a somatic deletion of 4 base pairs (bp) had occurred in APΔ3 sequences in these tumour cells.

Figure 3 shows the amplification by PCR of APΔ3 (*b*) and another sequence (APΔ2) containing an Alu repeat (*a*) from matched pairs of normal tumour DNAs. With the exception of cases 78 and 83, the bands corresponding to tumour tissue were a few nucleotides smaller than those from normal tissue. The detection of somatic deletions by AP-PCR implied that these mutations were very abundant, because of the random origin

† Present address: Institut de Recerca Oncologica, Hospital Duran i Reynals, Autovia de Castelldefels, Km 2,7 Hospitalet, 08907 Barcelona, Spain.
§ To whom correspondence should be addressed.

[CANCER RESEARCH 55, 1568–1570, April 1, 1995]

Advances in Brief

Replication Errors in Benign and Malignant Tumors from Hereditary Nonpolyposis Colorectal Cancer Patients[1]

Lauri A. Aaltonen,[2] Päivi Peltomäki, Jukka-Pekka Mecklin, Heikki Järvinen, Jeremy R. Jass, Jane S. Green, Henry T. Lynch, Patrice Watson, Gustav Tallqvist, Matti Juhola, Pertti Sistonen, Stanley R. Hamilton, Kenneth W. Kinzler, Bert Vogelstein, and Albert de la Chapelle

VOLUME 24 · NUMBER 33 · NOVEMBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer

Gershon Y. Locker, Stanley Hamilton, Jules Harris, John M. Jessup, Nancy Kemeny, John S. Macdonald, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

*7. Microsatellite Instability/*hMSH2 *or* hMLH1 *As Markers in Colorectal Cancer*

Note: This topic is new to the guideline.

2006 recommendation for use of microsatellite instability to determine prognosis. Microsatellite instability (MSI) ascertained by polymerase chain reaction (PCR) is not recommended at this time to determine the prognosis of operable colorectal cancer nor to predict the effectiveness of FU adjuvant chemotherapy.

ries.[108] Although there is suggestive evidence that MSI-H early-stage colon cancers have a more favorable prognosis than MSI-L or MSS tumors, the data are insufficient to recommend using MSI profile as an independent prognostic test for use in the clinic.

ed.[124] The contradictory conclusions may be an artifact of differences in the way FU was administered or the inclusion of rectal cancer in three series.[40,137,138] Nevertheless, the data reviewed do not support the use of MSI status in the prediction of benefit from FU chemotherapy as an adjunct to surgery for early-stage colorectal cancer at this time.

Cell, Vol. 75, 1027–1038, December 3, 1993, Copyright © 1993 by Cell Press

The Human Mutator Gene Homolog *MSH2* and Its Association with Hereditary Nonpolyposis Colon Cancer

Richard Fishel,* Mary Kay Lescoe,* M. R. S. Rao,†
Neal G. Copeland,† Nancy A. Jenkins,†
Judy Garber,‡ Michael Kane,§
and Richard Kolodner§

can give rise to mismatched ba
example, the deamination of 5
thymine and, therefore, a G·T r
1980). Second, misincorporat

Genetic mapping of a second locus predisposing to hereditary non-polyposis colon cancer

Annika Lindblom, Pia Tannergård, Barbro Werelius & Magnus Nordenskjöld

Mutation in the DNA mismatch repair gene homologue *hMLH1* is associated with hereditary non-polyposis colon cancer

C. Eric Bronner*, Sean M. Baker*, Paul T. Morrison†, Gwynedd Warren‡, Leslie G. Smith*, Mary Kay Lescoe§, Michael Kane‖, Christine Earabino†, James Lipford‖, Annika Lindblom¶, Pia Tannergård¶, Roni J. Bollag‡#, Alan R. Godwin‡#, David C. Ward‡**, Magnus Nordenskjold¶, Richard Fishel§, Richard Kolodner‖† & R. Michael Liskay*††

NATURE · VOL 368 · 17 MARCH 1994

Mutations of two *PMS* homologues in hereditary nonpolyposis colon cancer

Nicholas C. Nicolaides*, Nickolas Papadopoulos*, Bo Liu*, Ying-Fei Wei†, Kenneth C. Carter†, Steven M. Ruben†, Craig A. Rosen†, William A. Haseltine†, Robert D. Fleischmann‡, Claire M. Fraser‖, Mark D. Adams‡, J. Craig Venter‡, Malcolm G. Dunlop§, Stanley R. Hamilton‖, Gloria M. Petersen¶, Albert de la Chapelle#, Bert Vogelstein* & Kenneth W. Kinzler*††

* The Johns Hopkins Oncology Center, Baltimore, Maryland 21231, USA
† Human Genome Sciences, Inc., 9620 Medical Center Drive, Suite 300, Rockville, Maryland 20850-3338, USA
‡ The Institute for Genomic Research, 932 Clopper Road, Gaithersburg, Maryland 20878, USA
§ MRC Human Genetics Unit, Western General Hospital, Edinburgh EH4 2XU, UK
‖ The Johns Hopkins University School of Medicine, Departments of Pathology and Oncology, Baltimore, Maryland 21205, USA
¶ Department of Epidemiology, The Johns Hopkins University School of Public Health and Hygiene, Baltimore, Maryland 21205, USA
# Department of Medical Genetics, University of Helsinki, 00290 Helsinki, Finland

logy was within the amino-terminal segment, from codons 40 to 390, which was 30% identical between *yPMS1* and *hPMS1*, and 42% between *yPMS1* and *hPMS2* (Fig. 1*c*). This region contained several domains that are highly conserved among the *mutL*-related proteins, most notably the GFRGEAL domain which is perfectly conserved in E. coli and human *mutL* homologues[20]. A second region of significant homology was in the carboxyl terminus. This region was 22% identical between *yPMS1* and *hPMS1* and 47% identical between *yPMS1* and *hPMS2*, while very little homology was observed in this region between these proteins and the yeast *mutL*-homologue yMLH1 (not shown).

hPMS1 and *hPMS2* were previously localized to chromosomes 2 and 7, respectively[16]. To determine the precise location of these genes, genomic clones were used for fluorescent in situ hybridization (FISH) to human metaphase chromosome spreads. *hPMS1* was localized to chromosome 2q31-33 using a genomic P1 clone (1670) which contained its 5′ end (Fig. 2*a*, *b*, *c*). Likewise, the *hPMS2* gene was localized to chromosome 7p22 using a genomic P1 clone (2053) which contained the 3′ region of the *hPMS2* gene (Fig. 2*d*, *e*). Liskay and colleagues have also cloned a human *mutL* homologue which maps to chromosome 7 (R. M. Liskay, personal communication)[15]. Analysis with a variety of genomic clones indicates that *hPMS2* is a member of a subfamily which includes at least two related genes located on chromosome 7q.

To evaluate the role of *hPMS1* and *hPMS2* in HNPCC, we examined 40 patients with a family history of HNPCC. Eighteen were found to have mutations of *hMSH2* or *hMLH1* and therefore were not fully evaluated for *hPMS1* or *hPMS2* mutations[13,16,21]. To identify potential mutations in the other 22 samples, we employed an *in vitro* synthesized protein (IVSP) assay which detects deletions, insertions, frameshifts and non-

NATURE · VOL 371 · 1 SEPTEMBER 1994

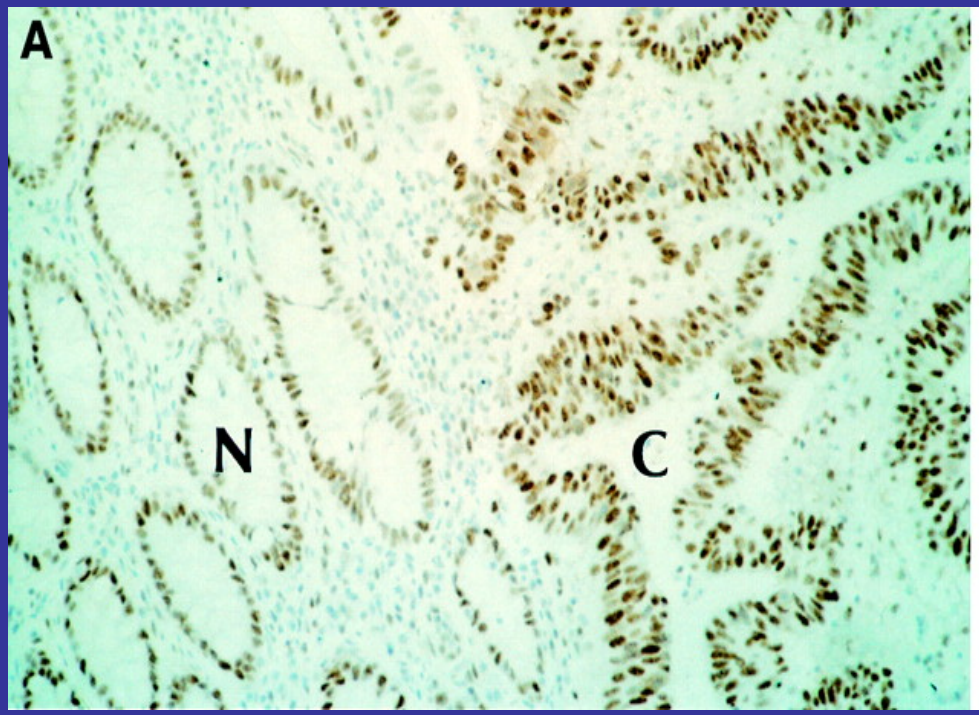
nature genetics volume 17 november 1997

Germline mutation of *MSH6* as the cause of hereditary nonpolyposis colorectal cancer

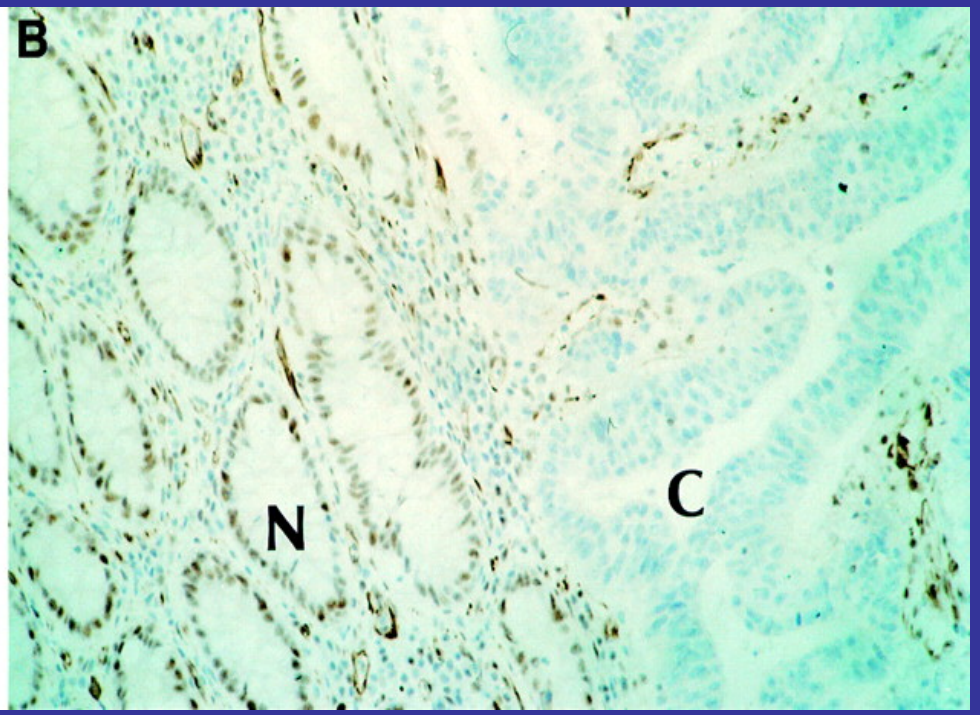
Michiko Miyaki[1,3], Motoko Konishi[1], Kiyoko Tanaka[1], Rei Kikuchi-Yanoshita[1], Masatoshi Muraoka[1], Masamichi Yasuno[2], Tohru Igari[3], Morio Koike[3], Mitsuro Chiba[4] & Takeo Mori[2]

[1]*Department of Biochemistry, Tokyo Metropolitan Institute of Medical Science, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113, Japan.* [2]*Department of Surgery and* [3]*Department of Pathology, Tokyo Metropolitan Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo113, Japan.* [4]*First Department of Internal Medicine, Akita University, Akita 010, Japan. Correspondence should be addressed to M.Mi.*

Analisi immunoistochimica delle proteine del Mismatch Repair



MSH2



MLH1

Journal of Clinical Oncology, Vol 19, No 19 (October 1), 2001: pp 3944-3950

Molecular Screening for Hereditary Nonpolyposis Colorectal Cancer: A Prospective, Population-Based Study

By Antonio Percesepe, Francesca Borghi, Mirco Menigatti, Lorena Losi, Moira Foroni, Carmela Di Gregorio, Giuseppina Rossi, Monica Pedroni, Elisa Sala, Fabiana Vaccina, Luca Roncucci, Piero Benatti, Alessandra Viel, Maurizio Genuardi, Giancarlo Marra, Paula Kristo, Paivi Peltomäki, and Maurizio Ponz de Leon

DISCUSSION

By a population-based approach to the HNPCC molecular diagnosis, the incidence of the disease in a high-incidence Western area for CRC was 0.3%, lower than any previous estimate, and the overall frequency of MSI was also as low as 8.3%. These two results will be discussed separately below.

Epidemiology of HNPCC:Frequency

Study	Evaluation	
	Clinical	Biomolecular
Mecklin (1987)	3.8-5.0%	-
Kee (1991)	1.0%	-
Stephenson (1991)	4.0%	-
Westlake	3.4%	-
Ponz de Leon (1993)	**2.6-4.5%**	-
Aaltonen (1998)	-	2.0%
Saalovara (2000)	-	2.8%
Peel (2000)	-	1.0%
Percesepe (2001)	-	**0.3%**
Kerber (2005)	3,1%	0,9%%

expressed as percent of all colorectal malignancies

Int. J. Cancer (Pred. Oncol.): **95,** 323–328 (2001)

Publication of the International Union Against Cancer

CLINICAL AND BIOLOGIC HETEROGENEITY OF HEREDITARY NONPOLYPOSIS COLORECTAL CANCER

Piero BENATTI[1]*, Luca RONCUCCI[1], Dorval GANAZZI[1], Antonio PERCESEPE[1], Carmela DI GREGORIO[2], Monica PEDRONI[1], Francesca BORGHI[1], Elisa SALA[1], Alessandra SCARSELLI[1], Mirco MENIGATTI[1], Giuseppina ROSSI[1], Maurizio GENUARDI[3], Alessandra VIEL[4] and Maurizio PONZ DE LEON[1]

MMR gene mutations and MSI are not found in all clinically diagnosed HNPCC families. We evaluated whether MMR genotyping and tumor MSI analysis could identify distinct clinical subgroups among HNPCC families. Twenty-nine clinical HNPCC families were divided into 3 groups: A, families with *hMLH1* or *hMSH2* gene mutations; B, MMR gene mutations not present but MSI present in at least 50% of tumors tested; C, mutational and MSI analyses negative. We evaluated tumor spectrum, age at onset, risk of cancer in the follow-up and survival for CRC in the 3 groups. Tumors of the target organs in HNPCC (colon and rectum, endometrium, ovary, small bowel, stomach, renal pelvis and ureter) were more frequent in the first 2 groups than in the latter. Colon cancer was more frequently located in the proximal colon and showed an earlier age at onset in families with MMR gene mutation or with MSI than in families with stable tumors. Comparing the occurrence of tumors in the follow-up, in the first 2 groups patients younger than 50 years had a higher RR, which was particularly marked for CRC (RR = 18.6 for group A *vs.* group C, RR = 16.7 for group B *vs.* group C). CRC patients in the first 2 groups had a better clinical prognosis. The results of molecular analysis could distinguish, within clinically defined HNPCC families, different subgroups to which specific programs of surveillance could be addressed.

Classificazione dei Tumori Colorettali Ereditari

(Ponz de Leon M, Bertario L, Genuardi M, Lanza G, et al.; Dis Col Rectum 2007)

HNPCC

Sindrome di Lynch

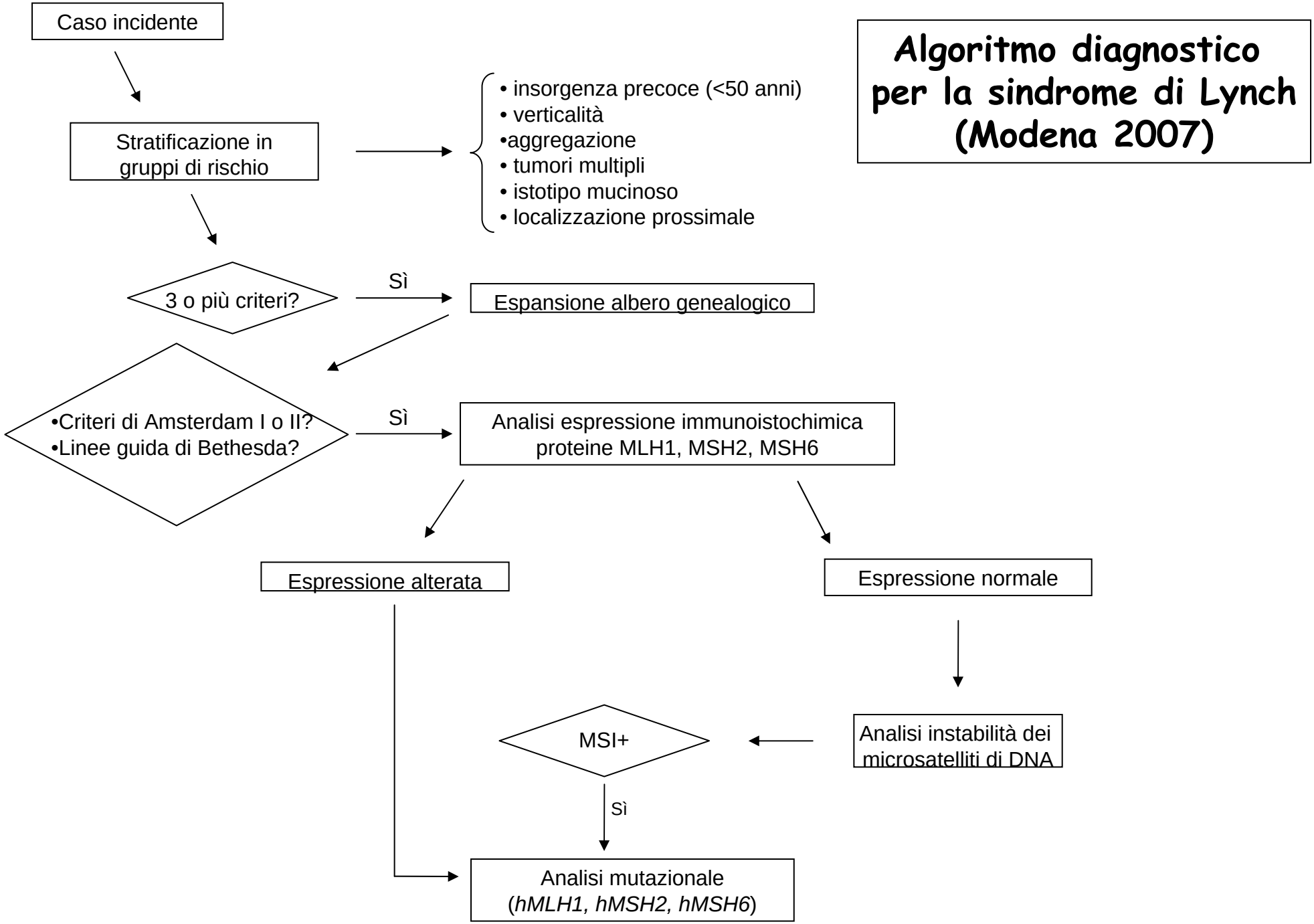
Evidenza documentata di alterazione del sistema del Mismatch repair

(mutazioni genetiche costituzionali, MSI-H, mancata espressione immunoistochimica della corrispondente proteina)

HNPCC clinica

Aggregazione di tumori maligni all'interno di un nucleo familiare tale da rientrare nei criteri di Amsterdam ma senza evidente alterazione del sistema del Mismatch repair

Algoritmo diagnostico per la sindrome di Lynch (Modena 2007)



UNIVERSITÀ DEGLI STUDI
DI MODENA E REGGIO EMILIA

ARTI
Associazione Ricerca Tumori
Intestinali

Associazione Italiana
per lo studio della Familiarità
ed Ereditarietà dei Tumori Gastrointestinali

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Regione Emilia Romagna

CANCRO COLORETTALE EREDITARIO
(SINDROME DI LYNCH)

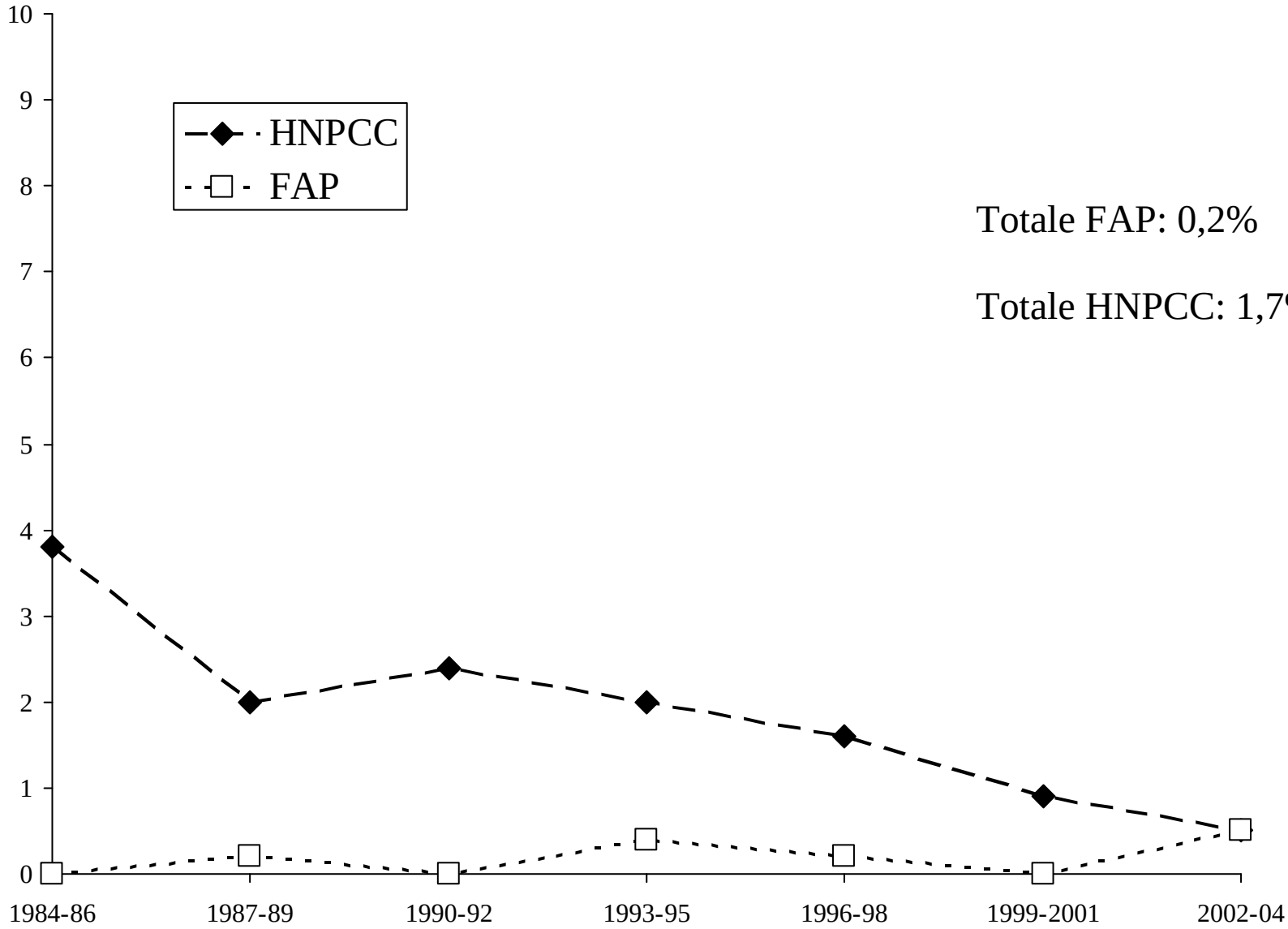
L'esperienza del Gruppo di Studio sui tumori colorettali dell'Università degli studi di Modena e Reggio Emilia e dell'Azienda Policlinico

M. PONZ DE LEON, P. BENATTI, A. PEZZI, L. RONCUCCI,
C. DI GREGORIO, L. LOSI, R. SASSATELLI, G. ROSSI, G. PONTI,
M. PEDRONI, S. MAFFEI, B. RONCARI, E. BORSI, F. ROSSI,
M. MENIGATTI, F. DOMATI, C. DE GAETANI.

QUADRO GENERALE HNPCC (1984-2007)

Famiglie con HNPCC	65
Famiglie valutate	57 (87,7%)
Famiglie con Mutazioni costituzionali (Sindrome di Lynch)	32 (49,2%)
hMLH1	15
hMSH2	13
hMSH6	4
"Gene Carriers asintomatici"	15

Frequenza di cancri colorettali HNPCC e FAP nel periodo 1984-2004



HNPCC e *hMLH1*

- Età d'insorgenza più precoce rispetto a pazienti con mutazioni di altri geni.
- Più frequente localizzazione nel colon destro.
- Maggior rischio di tumori multipli colorettali.
- Minor frequenza di neoplasie extracoliche ad eccezione di neoplasie endometriali e gastriche.

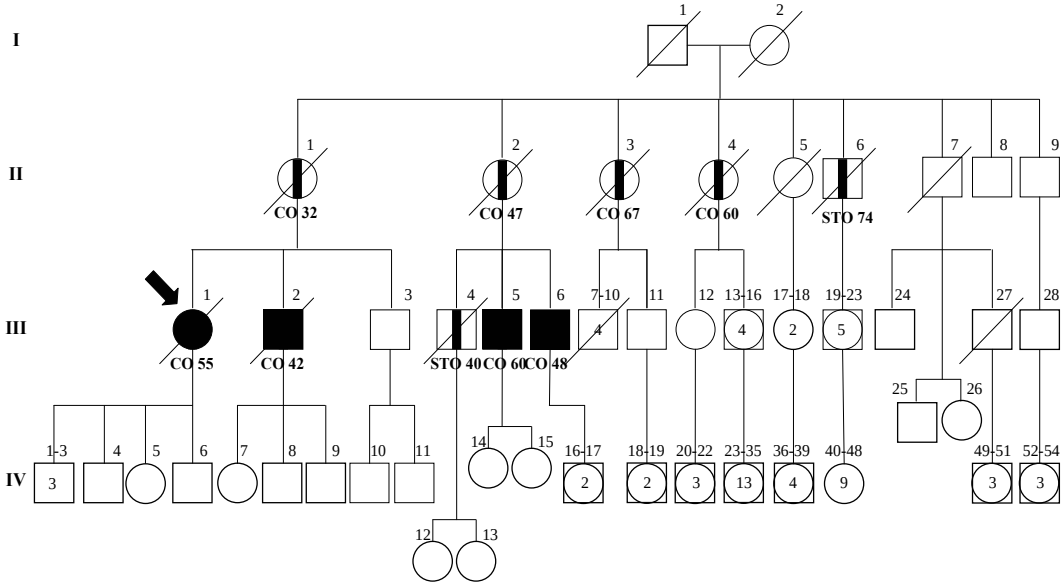
Ponz de Leon et al., Scand J Gastroenterol, 2007

Mutazioni costituzionali del gene *hMLH1* osservate in famiglie con S. di Lynch (1984-2007)

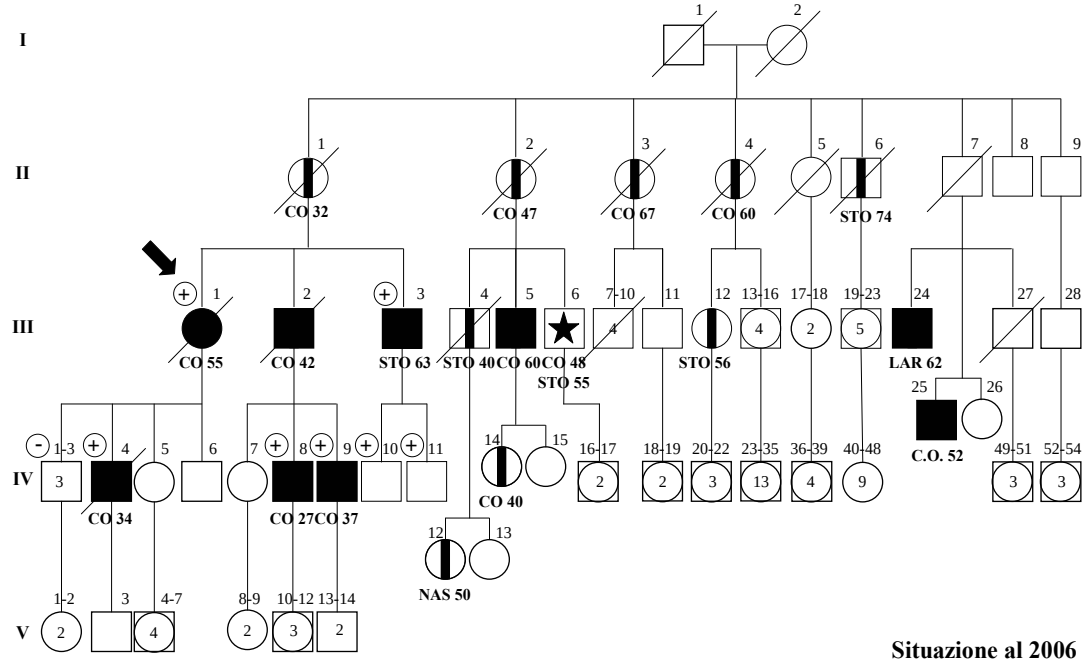
Famiglie	Mutazione	Conseguenza	MSI	IHC MLH1
1-4-6-8-9-30	*Ins T 2269- 2270 Codone 757, Esone 19	Allungamento proteina 33 aa	+	-
3	+5 Introne 17; G→C	Delezione Esone 17	+	-
7	CTA→CCA 2246 Codone 749, Esone 19	Missenso (Significato da chiarire)	+	+ -
10	+1 Introne 13; G→T	Delezione Esone 13	+	-
15	Ins T 1542-1543 Codone 514, Esone 13	Proteina tronca	+	-
16	GCT→ACT 2041 Codone 681, Esone 18	Missenso (riportata in letteratura)	+	-
17	TCG→TAG 2084 Codone 695, Esone 18	Proteina tronca	+	-
21	CGA→TGA 1459 Codone 487, Esone 13	Proteina tronca	+	-
23	Del AATC 727 Codone 243, Esone 9	Proteina tronca	+	-
24	Del GGGA 1952 Codone 651, Esone 17	Proteina tronca	+	-

*: founder mutation

HNPCC e *hMLH1*



Situazione Iniziale (1991)

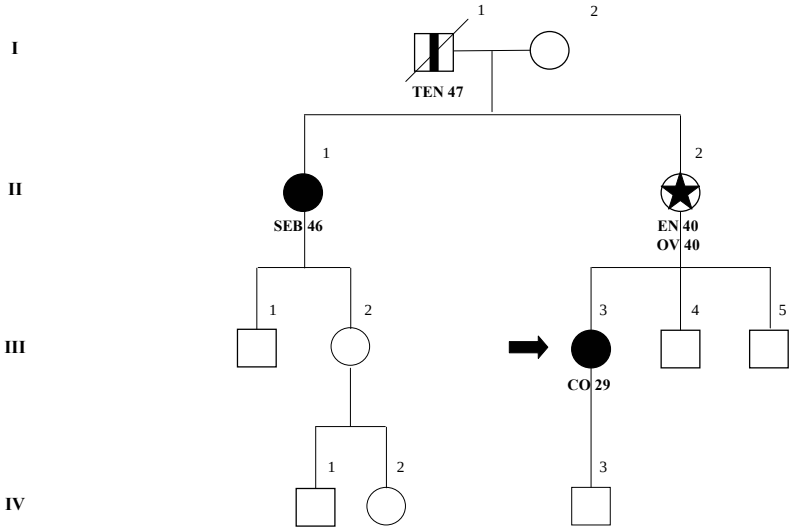


Situazione al 2006

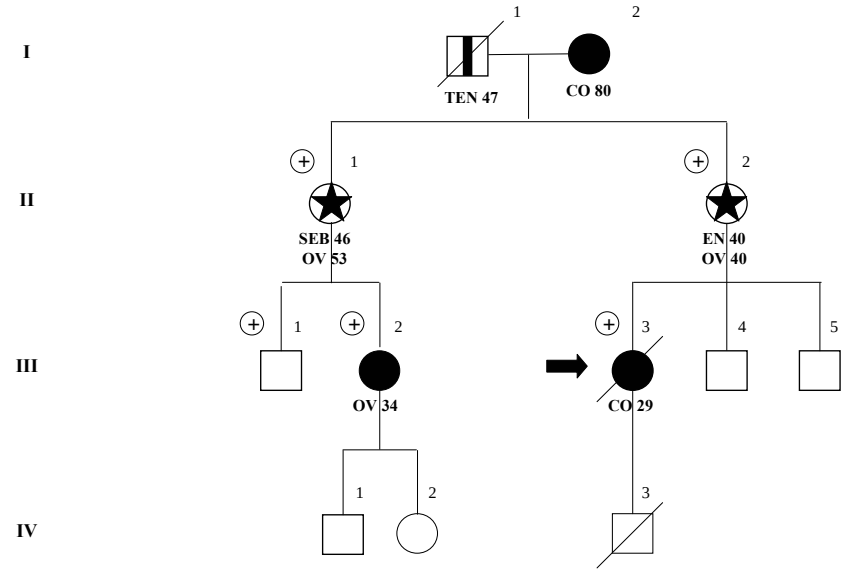
HNPCC e *hMSH2*

- Età d'insorgenza più tardiva delle neoplasie coliche, più precoce nelle extracoliche (*Peltomaki P,Fam Cancer 2001)*
- Maggior frequenza di tumori extracolici *(Vasen H, JCO 2006)*
- Nelle donne, il rischio di sviluppare tumori extracolici è superiore a quello di sviluppare neoplasie colorettali *(Lin W,* J Gastrointest Surg *1998)*
- Più frequentemente coinvolto nella sindrome di Muir-Torre *(Ponti G, Lancet Oncol 2006)*

HNPCC e *hMSH2*



Situazione Iniziale (2000)

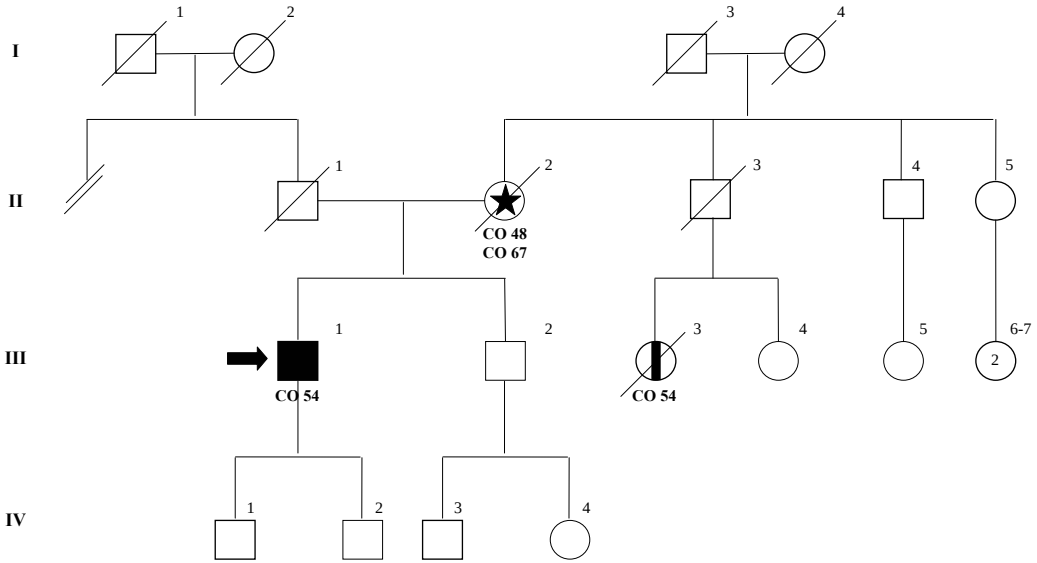


Situazione al 2006

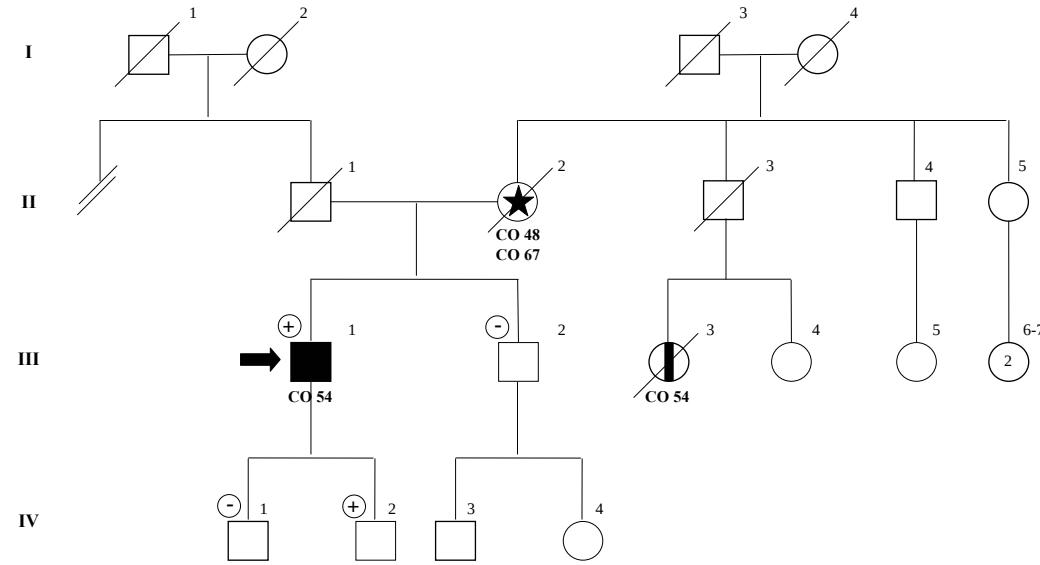
HNPCC e *hMSH6*

- Fenotipo meno aggressivo rispetto alle forme causate da mutazioni di hMLH1 e hMSH2
- Penetranza incompleta
- Età d'insorgenza più tardiva
- Tumori extracolici frequenti
- Instabilità dei microsatelliti non costante

HNPCC e *hMSH6*



Situazione Iniziale (1994)



Situazione al 2006

CARATTERISTICHE CLINICHE DELLA SINDROME DI LYNCH IN RELAZIONE AL GENE MUTATO

Sede neoplastica	***hMLH1***		***hMSH2***		***hMSH6***	
	% del totale	Età media (anni)	% del totale	Età media (anni)	% del totale	Età media (anni)
Colon-retto	62.5	47	43.7	49	66.7	57
Sedi HNPCC correlate*	25.0	50	39.1	50	20.0	44
Sedi extra HNPCC	12.5	57	17.2	51	13.3	70
Totale	100	49	100	49	100	55

*: Endometrio, stomaco, pelvi renale-uretere, ovaio, tenue, pancreas, vie biliari, lesioni sebacee, encefalo $$

FOLLOW UP DELLE FAMGLIE CON SINDROME DI LYNCH IN RELAZIONE AL GENE MUTATO

	hMLH1	***hMSH2***	***hMSH6***
Sede neoplastica	% del totale	% del totale	% del totale
Colon-retto	52.1	29.7	100
Sedi HNPCC correlate*	26.9	56.1	-
Sedi extra HNPCC	21.0	14.2	-
Totale	100	100	100

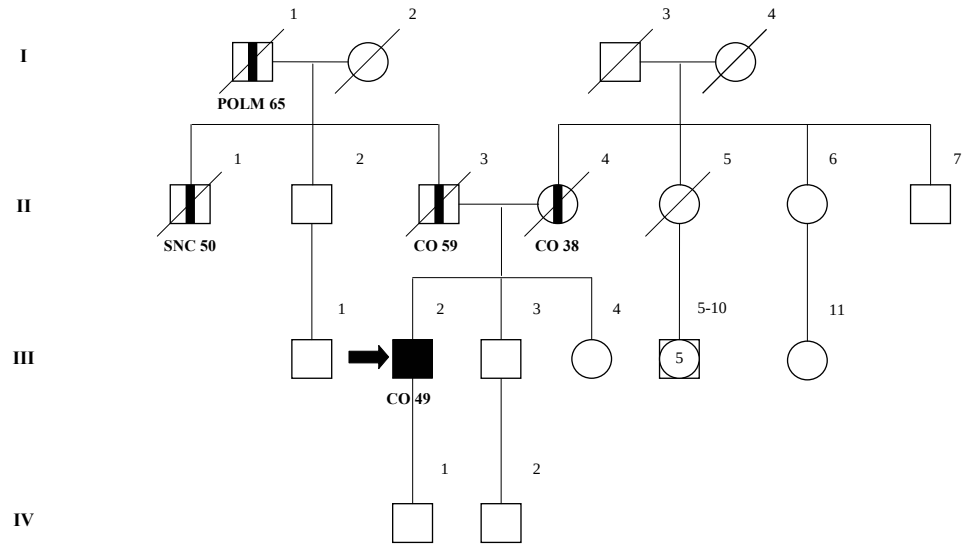
*: Endometrio, stomaco, pelvi renale-uretere, ovaio, tenue, pancreas, vie biliari, lesioni sebacee, encefalo $$

Sindrome di Muir-Torre

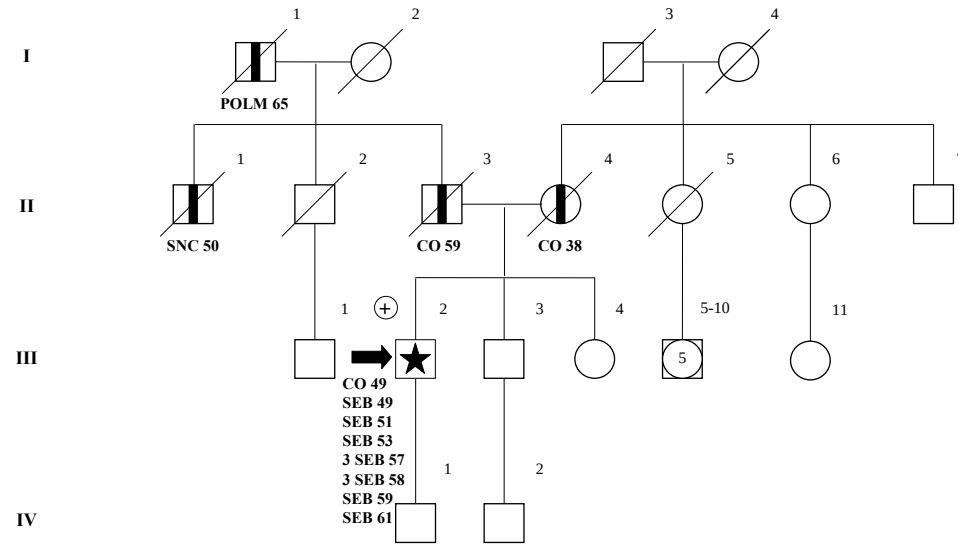
- Genodermatosi caratterizzata dall'associazione tra tumori viscerali e lesioni dermatologiche di natura sebacea (adenomi, carcinomi) e/o keratoacantomi.

- Variante della sindrome di Lynch.

Sindrome di Muir-Torre



Situazione Iniziale (1989)



Situazione al 2006

LA FOUNDER MUTATION

- In sei famiglie (tre del registro, tre di aree limitrofe) è stata identificata la stessa mutazione.
- Questa consiste nell'inserzione di una T in una posizione 2269-70 (codone 757, esone 19, gene MLH1) che causa allungamento della proteina e sua instabilità.
- I tumori mostrano instabilità dei microsatelliti e mancata espressione della proteina codificata da *hMLH1*.
- La segregazione nelle famiglie, l'area di origine, il fatto di non essere stata riportata in letteratura depongono per una Founder Mutation.

Caluseriu et al., Journal of Medical Genetics, 2004

LA FOUNDER MUTATION: caratteristiche cliniche

SEDE CRC (%)	FOUNDER MUTATION	MLH1	MSH2	MSH6
Colon dx	68,6	70,0	52,9	50,0
Colon sx	9,8	20,0	29,5	0,0
Retto	**21,6**	10,0	17,6	50,0
Totale	100	100	100	100

SEDE	FOUNDER MUTATION	MLH1	MSH2	MSH6
CRC	59,3	66,7	43,2	66,7
HNPCC relato	25,9	23,8	39,7	20,0
Extra HNPCC	14,8	9,5	17,1	13,3
Totale	100	100	100	100

Genotype-phenotype correlations in individuals with a founder mutation in the MLH1 gene and hereditary non-polyposis colorectal cancer

MAURIZIO PONZ DE LEON[1], PIERO BENATTI[1], CARMELA DI GREGORIO[2], LORENA LOSI[3], MONICA PEDRONI[1], GIOVANNI PONTI[1], MAURIZIO GENUARDI[4], ALESSANDRA VIEL[5], EMANUELA LUCCI-CORDISCO[4], GIUSEPPINA ROSSI[1] & LUCA RONCUCCI[1]

Table V. Multiple tumours in the three investigated groups versus sporadic malignancies of the large bowel.

	Groups			
	Founder	MLH1	MSH2	Sporadic° colorectal cancer
Patients with cancer	70	53	92	3.818
Patients with multiple tumours	18 (25.7%)*	11 (20.1%)*	12 (13.0%)*	398 (10.4%)*
Patients with 3 tumours	2	0	1	–
Patients with 4 or more tumours	3	0	0	–

*The frequency of multiple tumours was significantly higher (by Z test) in the founder mutation group ($p < 0.001$) and in the MLH1 group ($p < 0.005$) versus sporadic neoplasms; °data from the Colorectal Cancer Registry of Modena 1984–2004.

LA FOUNDER MUTATION:
sviluppi futuri

- Identificazione progenitore comune
- Identificazione soggetti a rischio
- Screening biomolecolare in tutti i soggetti con cancro colorettale ad età precoce (immunoistochimica)

CONCLUSIONI

1) Grazie all'esistenza di un Registro Tumori specializzato per il colon-retto è stato possibile elaborare un approccio clinico-biomolecolare per diagnosticare le sindromi ereditarie di cancro colorettale nella popolazione generale.

- Tra i tumori ereditari colorettali, l'HNPCC rappresenta la sindrome più frequente, costituendo quasi il 2% del totale dei cancri colorettale.

- Dal 1984 ad oggi sono state identificate, 65 famiglie con HNPCC: di queste 32 risultano portatrici di mutazione: 15 di hMLH1, 13 di hMSH2 e 4 di hMSH6.

- Nel territorio modenese-reggiano è stata identificata una mutazione del gene *hMLH1* con effetto fondatore: questo potrebbe consentire screening mirati in pazienti con cancro colorettale con caratteristiche sospette per sindromi ereditarie.

SVILUPPI FUTURI

1) Identificazione dell'origine della mutazione founder

2) Screening bimolecolare nella popolazione di soggetti con cancro colorettale con caratteristiche sospette per forme ereditarie, residenti nel territorio reggiano-modenese

3) Caratterizzazione biomoecolare delle famiglie con HNPCC clinica senza mutazione dei geni maggiori del MMR: PMS2? altri geni?

4) Analisi dell'interazione ambiente-genotipo-fenotipo

Università di Modena e Reggio Emilia

Dip. di Medicine e Specialità Mediche

- Maurizio Ponz de Leon
- Piero Benatti
- Annalisa Pezzi
- Luca Roncucci
- Giuseppina Rossi
- Monica Pedroni
- Stefania Maffei
- Barbara Roncari
- Enrica Borsi
- Federica Rossi
- Federica Domati
- Giovanni Ponti
- Mirco Menigatti

Dip. di Servizi diagnostici, di Laboratorio e Medicina Legale

- Carmela De Gaetani
- Lorena Losi

Azienda USL di Modena

Dip. Patologia Clinica, Osp. Carpi

- Carmela Di Gregorio

Azienda USL di Reggio nell'Emilia

Servizio Endoscopia Digestiva, ASMN RE

- Romano Sassatelli

Università di Modena e Reggio Emilia

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Piero Benatti
Annalisa Pezzi
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Lorena Losi

Azienda USL di Modena

Dip. Patologia Clinica, Osp. Carpi
Carmela Di Gregorio

Azienda USL di Reggio nell'Emilia

Servizio Endoscopia Digestiva, ASMN RE
Romano Sassatelli

Familial Cancer (2005) 4: 211–218
DOI 10.1007/s10689-004-4489-x

Evolution of the nomenclature for the hereditary colorectal cancer syndromes

C. Richard Boland
Division of Gastroenterology, Medical Center, Baylor University, Dallas, Texas, USA

Naming hereditary colorectal cancer

The diagnosis of Lynch syndrome is currently made on the basis of a germline mutation in a DNA MMR gene, rather than by the characteristics of the family history.

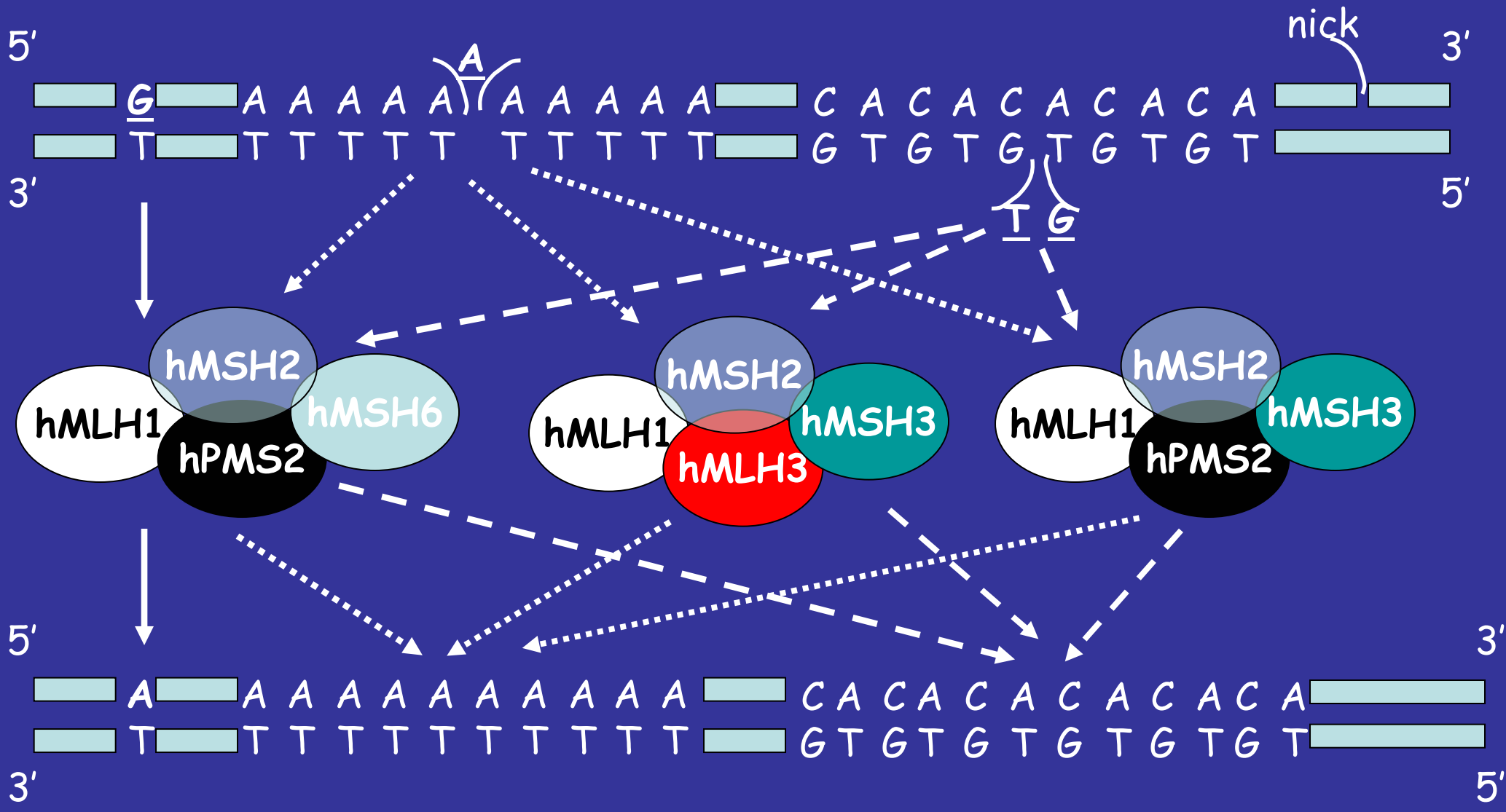
Finally, familial clusters of colon cancer, including some with colon cancers before age 50, will not have MSI in their tumors, will not be linked to defects in DNA MMR, and should be distinguished from those with germline defects in DNA MMR genes. These MMR genes. However, no final conclusion regarding this name was incorporated into any of the proceedings reported from these meetings, in spite of the efforts of several of the participants.

L'Instabilità dei Microsatelliti (MSI)

- Espressione fenotipica dell' alterazione del sistema del Mismatch Repair.
- MSI è presente nel 95% dei tumori HNPCC e nel 15% dei tumori colorettali sporadici.
- MSI si osserva più frequentemente in pazienti con età inferiore ai 45 anni o con età superiore ai 70.
- Relazione con la sede prossimale, l'istotipo mucinoso, il grading scarsamente differenziato, il contenuto di DNA tumorale diploide.
- Marcatore prognostico?
- Sensibilità alla chemioterapia?

- Marcatore di screening per le forme ereditarie da mutazioni costituzionali dei geni del MMR

Proteins involved in mismatch repair



Jiricny et al, Curr Opin Genet Dev 2000

Familial Cancer (2005) 4: 239–244
DOI 10.1007/s10689-005-0657-x

Frequency of familial colon cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) in a large population database

Richard A. Kerber[1], Deborah W. Neklason[1], Wade S. Samowitz[2], and Randall W. Burt[3,4],

Nomenclature

Based on the finding that a substantial fraction of Amsterdam I and II families were not found to be tumor MSI positive, we propose that the terms HNPCC or Lynch syndrome only be applied to those families with an identified, disease causing mutation of one of the mismatch repair genes. Amsterdam I and II criteria are already explicitly defined. But it should be understood that families that meet these criteria may well not have HNPCC, as demonstrated in the present study.

"Familial colon cancer" is a nonspecific term, but one that is frequently used. The term inherently includes all defined or suspected cases of inherited colon cancer, but also "chance" familial clusters, and clusters arising from common environmental exposures in a family. Any limitation of the definition of this term would seem counterintuitive.

But we would propose one additional term for utility in dealing with familial colon cancer, both investigationally and clinically. This term is, "high-risk familial colon cancer." The definition, as used in this investigation, would include: any first-degree relative pair with colon cancer or any person with a colon cancer diagnosis under

REVIEW

Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer)

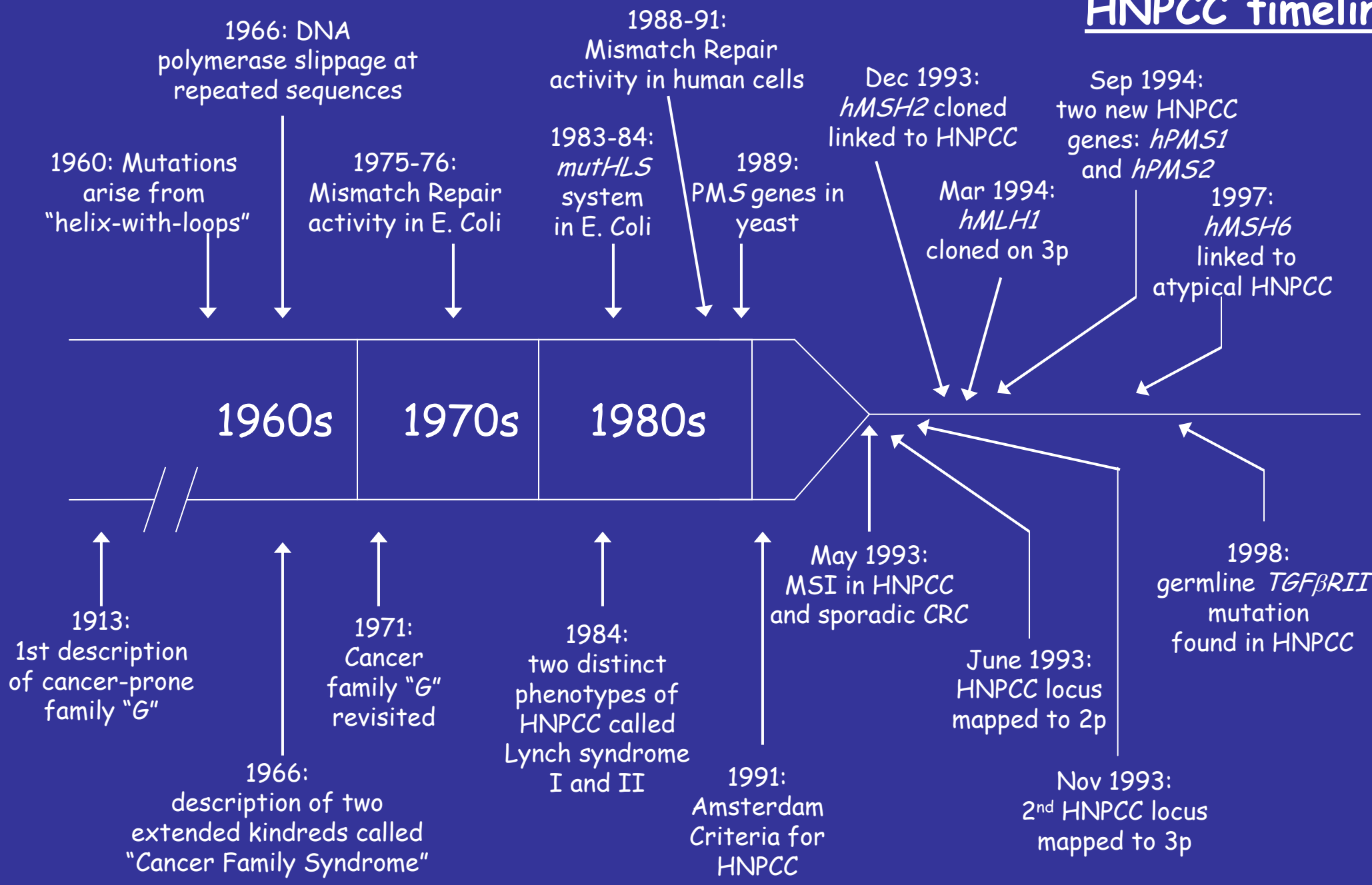
H F A Vasen, G Möslein, A Alonso, I Bernstein, L Bertario, I Blanco, J Burn, G Capella, C Engel, I Frayling, W Friedl, F J Hes, S Hodgson, J-P Mecklin, P Møller, F Nagengast, Y Parc, L Renkonen-Sinisalo, J R Sampson, A Stormorken, J Wijnen

J Med Genet 2007;**44**:353–362. doi: 10.1136/jmg.2007.048991

TERMINOLOGY

Various names for Lynch syndrome have been used in the past century. A workshop in Amsterdam in 1989 agreed upon the name "HNPCC", because at that time the syndrome was unknown to most doctors. This name clarified that the syndrome described an inherited form of CRC. The appropriateness of the name was discussed again at an international meeting in Bethesda in 2004. Most participants considered the term HNPCC to be inappropriate, since the syndrome is also associated with many other tumours. It was proposed that the name "Lynch syndrome" should be reintroduced, and that this name should be reserved for families with strong evidence of MMR deficiency—for example, by the presence of an MMR defect or by the presence of MSI in tumours.[15] The European group agreed that this name is the best available name for the syndrome. The group suggests that families that meet the original Amsterdam criteria but do not have evidence for MMR deficiency are referred to as having familial CRC.

HNPCC timeline



" Who could have predicted that a bacterial mismatch-binding protein might save human lives?"

(Joseph Jiricny, 1994)

Mutazioni costituzionali del gene *hMSH2* osservate in famiglie con S. di Lynch (1984-2007)

Famiglia	Mutazione	Conseguenza	MSI◊	IHC*	
				MSH2	MSH6
2	Del CCTA 1243; Codone 415, Esone 7	Proteina tronca	+	-	-
5-12	+3 Introne 5; A→T	Delezione Esone 5	+	-	-
10	TGG→TGA 1034; Codone 345, Esone 6	Proteina tronca	+	-	-
13	Del A 2647; Codone 883, Esone 16	Proteina tronca	+	-	-
18	Del TT 880; Codone 294, Esone 5	Proteina tronca	+	-	-
19	GAA →TAA, Codone 290, Esone 5	Proteina tronca	+	-	-
20	Del AAT 1786; Codone 596, Esone 12	Perdita di un aminoacido	+	-	-
22	Ins A 2362-2363; Codone 788, Esone 14	Proteina tronca	+	-	-
25	GGC→GAC 2005; Codone 669, Esone 13	Missenso	+	-	-
26	GCA→CCA 2286, Codone 762, Esone 14	Missenso (Significato da chiarire)	+	-	+
31 (MT1)	Del Esone 1	Proteina tronca	+	-	-
32 (MT2)	GCA→TGA 2133; Codone 711, Esone 13	Proteina tronca	+	-	+

Mutazioni costituzionali del gene *hMSH6* osservate in famiglie con S. di Lynch (1984-2007)

Famiglia	Mutazione	Conseguenza	MSI◊	IHC
				MSH6
14	Del A 2984 Codone 995, Esone 4	Proteina tronca	+	-
28	Del AGG Codone 385, Esone 4	Perdita di un aminoacido	+	-
29	Del CGT Codone 1242, Esone 8	Perdita di un aminoacido	+	-
27	Del TT 3098 Codone 1032, Esone 4	Proteina tronca	+	-

ANALISI IMMUNOISTOCHIMICA DELLE PROTEINE MLH1, MSH2 E MSH6 NELLA DIAGNOSI DI HNPCC

- **VANTAGGI**:
  - il test può essere eseguito su preparati istologici paraffinati;
  - in presenza di sospetto clinico di forma familiare, la mancata espressione di una specifica proteina può indirizzare direttamente alla sequenza di un determinato gene;
  - particolarmente utile nella ricerca di mutazioni di *hMSH6*.

- **PROBLEMI**: le proteine potrebbero essere normalmente espresse nonostante la presenza di mutazioni germinali; ciò può accadere per:
  - produzione di proteine di normale lunghezza che, sebbene non funzionali, possono essere identificate dall'anticorpo utilizzato;
  - produzione di frammenti proteici stabili che possono essere anch'essi identificati dall'indagine immunoistochimica.

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