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HNPCC, molecular and clinical dilemmas

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Citation

Wagner, A. (2005, April 27). *HNPCC, molecular and clinical dilemmas*. Macula, Boskoop.
Retrieved from <https://hdl.handle.net/1887/2719>

Version: Corrected Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

**HNPCC,
Molecular and Clinical Dilemmas**

Anja Wagner



**HNPCC,
Molecular and Clinical Dilemmas**

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden
op gezag van de Rector Magnificus Dr. D.D. Breimer,
hoogleraar in de faculteit der Wiskunde en
Natuurwetenschappen en die der Geneeskunde,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 27 april 2005
te klokke 15.15 uur

door

Anja Wagner
geboren te Rotterdam
in 1968

Promotiecommissie

Promotor.	Prof. Dr. R. Fodde
Co-promotor.	Dr. E.J. Meijers-Heijboer (Erasmus MC, Rotterdam)
Referent.	Prof. Dr. J. Burn (University of Newcastle, UK)
Overige leden.	Prof. Dr. G.J. van Ommen Dr. J. Morreau

Cover design/ lay-out: Jan and Anja Wagner

Graphical support: Tom de Vries Lentsch

Printed by: Drukkerij Macula, Boskoop, the Netherlands

ISBN 90-9019216-6

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The studies described in this thesis were performed at the Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, and the Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, the Netherlands. The publication of this thesis, and the studies described in it were financially supported by the Dutch Cancer Society, the Department of Human and Clinical Genetics, Leiden University Medical Center, Leiden, and the Department of Clinical Genetics, Erasmus University Medical Center, Rotterdam, the Netherlands.

Onvergeeflijk is het, dat de mensen dromen hebben
en ze niet waarmaken!
En toch, hoop vervliegt elke dag en overal
In elke kamer. Ieder bed.
Op mijn reizen heb ik dit duidelijk gezien:
Iedere ontmoeting, elk gesprek brengt mensen verder af
van wat zij willen.
Zij vertrouwen niet op wat zij zijn,
maar op hoe zij worden gezien.

Arthur Japin

Voor mijn ouders

In herinnering aan Ondiene en aan mijn patiënten die stierven aan kanker

Contents

Aims and outline of the thesis	9
 Chapter 1. Introduction	
1.1 Hereditary Non Polyposis Colorectal Cancer (HNPCC)	13
1.2 History	13
1.3 The HNPCC genes and their protein products	15
1.4 Candidate genes	19
1.5 The HNPCC gene mutation spectra	20
1.6 Molecular basis of tumour initiation and progression in HNPCC	21
1.7 Cancer risks	31
1.8 HNPCC tumours: histopathologic features	34
1.9 Microsatellite Instability (MSI)	34
1.10 Prognosis	35
1.11 Screening	36
1.12 Prevention	40
1.13 Differential diagnosis	41
1.14 Molecular diagnostics of HNPCC	43
1.15 Selection for mutation analysis	47
1.16 Genetic counselling	52
 Chapter 2. Molecular genetic studies in HNPCC	
2.1 Molecular Analysis of Hereditary Non-Polyposis Colorectal Cancer (HNPCC) in the USA: High Mutation Detection Rate among Clinically Selected Families and Characterisation of an American Founder Deletion in the <i>MSH2</i> Gene. <i>Am J Hum Genet</i> 2003;72;1088-1100.	57
2.2 A Founder Mutation of the <i>MSH2</i> Gene and Hereditary Nonpolyposis Colorectal Cancer in the United States. <i>JAMA</i> 2004;291;718-724.	73

2.3	A 10-Mb Paracentric Inversion of Chromosome arm 2p Inactivates <i>MSH2</i> and is Responsible for Hereditary Non Polyposis Colorectal Cancer in a North-American Kindred. <i>Genes Chromosomes Cancer</i> 2002;35;49-57.	83
 Chapter 3. Clinical studies in HNPCC		
3.1	Atypical HNPCC owing to <i>MSH6</i> germline mutations: analysis of a large Dutch pedigree. <i>J Med Genet</i> 2001;38;318-322.	97
3.2	Cancer Risk in Hereditary Nonpolyposis Colorectal Cancer Due to <i>MSH6</i> Mutations; Impact on Counselling and Surveillance. <i>Gastroenterology</i> 2004;127;17-25.	105
3.3	Genetic testing in hereditary non-polyposis colorectal cancer families with a <i>MSH2</i> , <i>MLH1</i> , or <i>MSH6</i> mutation. <i>J Med Genet</i> 2002;39;833-837.	117
3.4	Long term follow-up of HNPCC gene mutation carriers; compliance with screening and satisfaction with counselling and screening procedures. <i>Accepted for publication in Familial Cancer</i> 2005:4.	125
 Chapter 4. Discussion		
 References		
Summary		
Samenvatting		
List of tables and figures		
Curriculum vitae		
List of publications		

Aims and outline of the thesis

Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is the main inherited predisposition to colorectal cancer. Major features of HNPCC are colorectal and endometrial cancers. Tumours of the ovaries, stomach, small bowel, biliary tract, urinary tract, skin and brain occur at lower frequencies. Mutations in at least 4 different mismatch repair (MMR) genes are responsible for HNPCC, namely *MSH2* and *MLH1* in the majority of cases and, more rarely, *MSH6* and *PMS2*. In previous studies, *MSH2* and *MLH1* mutations were found in 45-64% of the families with HNPCC⁷³.

In **Chapter 2**, we questioned whether unresolved HNPCC families were due to a lack of sensitivity of *MSH2* and *MLH1* mutation detection techniques, or to mutations of *MSH6* or other genes. To this aim, we thoroughly investigated a cohort of 59 US HNPCC families, clinically selected by Prof. Henry Lynch, for the presence of point mutations and genomic rearrangements in the *MSH2*, *MLH1* and *MSH6* genes. We identified a North American founder mutation, a deletion of *MSH2* exons 1-6, common to 12% of the cohort. The birthplace of the eldest ancestor carrying this founder mutation could be traced back to 18th century Germany. Additionally we detected a 10-Mb paracentric inversion inactivating the *MSH2* gene.

The clinical cancer phenotype associated with mutations of *MSH6* is less well defined when compared to *MLH1* and *MSH2*. In **Chapter 3.1** and **3.2**, we analysed a large Dutch pedigree and a cohort of 20 *MSH6* mutation positive families to calculate the cumulative age-specific risks of colorectal cancer and endometrial cancer, and compared the outcomes with the cancer risks in *MSH2* and *MLH1* mutation carriers. Based on the findings, we formulated *MSH6*-tailored screenings and preventative options.

The detection of a germline mutation in *MSH2*, *MLH1* or *MSH6* in an individual enables predictive genetic testing of at-risk relatives. In **Chapter 3.3**, we analysed the demand for genetic testing of members of 18 Dutch families with a known mutation in *MSH2*, *MLH1* or *MSH6*. Regular colonoscopy reduces the overall mortality by 65% in members of families with HNPCC¹¹⁷. It is therefore of utmost importance that mutation carriers adhere to surveillance protocols. We evaluated (**Chapter 3.4**) the impact of genetic testing on the adherence to cancer surveillance protocols. Simultaneously, we investigated the satisfaction with cancer screening and genetic testing procedures in 70 proven mutation carriers at the long term.

The studies described in this thesis contribute to the understanding of the molecular genetic aetiology of HNPCC, and add to evidence-based clinical care for HNPCC families.

