Acta Biochimica Polonica

Vol. 49 No. 3/2002

571–581

QUARTERLY

Review

Molecular basis of inherited predispositions for tumors★

Jan Lubiński[1], Bohdan Górski[1], Grzegorz Kurzawski[1], Anna Jakubowska[1], Cezary Cybulski[1], Janina Suchy[1], Tadeusz Dębniak[1], Ewa Grabowska[2]✉, Marcin Lener[2] and Katarzyna Nej[2]

[1]*Hereditary Cancer Centre, Department of Genetics and Pathology, Pomeranian Academy of Medicine, Szczecin, Poland;* [2]*Inter-University Unit of Molecular Biology, University of Szczecin and Pomeranian Academy of Medicine, Szczecin, Poland*

Received: 22 April, 2002, revised: 16 July, 2002; accepted: 25 August, 2002

Key words: *BRCA1, BRCA2, MSH2, MLH1,* inherited tumors, gene interactions

On the basis of literature data and own experience the authors review the current knowledge about the molecular basis of inherited predispositions for tumors. They hypothesize that in the near perspective 5–10 years studies using existing registry data/material and the latest novel technology will allow the identification of the molecular background for the majority of hereditary cancers which will have enormous practical consequences especially for the prevention of malignancies.

CONSTITUTIONAL MUTATIONS IN GENES RELATED TO PREDISPOSITION FOR TUMORS

It is now well recognized that 5–10% of all tumors including so-called common malignancies such as cancers of the breast, colon and ovaries occur as a result of high monogenic predispositions. It is estimated that an additional 30–50% of malignancies are also „inherited tumors", however they occur due to polygenic predispositions. The molecular basis of polygenic tumors is not known, although its existence is strongly suggested by results of studies on monozygotic twins. In contrast, monogenic background has already been proven for a significant proportion of hereditary cancers (Lichtenstein *et al.*, 2000).

★Presented at the XXXVII Meeting of the Polish Biochemical Society, Toruń, Poland, September, 10–14, 2001.

✉Correspondence and requests for reprints should be addressed to: Ewa Grabowska, Inter-University Unit of Molecular Biology, Połabska 4, 70-115 Szczecin, Poland; tel.: (48 91) 466 15 44; fax.: (48 91) 466 1533; e-mail: ewagrabowska@interia.pl

Abbreviations: HNPCC, hereditary non-polyposis colorectal cancer.

Genes/syndromes most frequently examined for the occurrence of constitutional mutations are summarized in Table 1.

Although the number of known genes related to cancer predisposition with detected unequivocal constitutional mutations has

Table 1. Genes/syndromes most frequently examined for the occurrence of constitutional mutations

Gene	Syndrome	Predisposition to tumors	References
BRCA1	Hereditary Breast-Ovarian Cancer, BRCA1 type	breast, ovary	de los Rios *et al.*, 2001; Górski *et al.*, 2000; Jakubowska *et al.*, 2001
BRCA2	Hereditary Breast-Ovarian Cancer, BRCA2 type	breast, ovary	de los Rios *et al.*, 2001
ERBB2	Familial Clustering of Breast Cancer	breast	McKean-Cowdin *et al.*, 2001
ESR	Familial Clustering of Breast Cancer	breast	Anderson *et al.*, 1997
ATM	Ataxia Telangiectasia	leukemia, breast	Broeks *et al.*, 2000
MSH2	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Dębniak *et al.*, 2001; Jakubowska *et al.*, 2001a; Kurzawski *et al.*, 2002a; Park *et al.*, 1999; Peltomäki *et al.*, 1997
MLH1	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Dębniak *et al.*, 2001; Jakubowska *et al.*, 2001a; Kurzawski *et al.*, 1999; Kurzawski *et al.*, 2002a; Park *et al.*, 1999; Peltomäki *et al.*, 1997
MSH6	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Berends *et al.*, 2002; Huang *et al.*, 2001
MSH3	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Huang *et al.*, 2001
PMS1	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Olschwang, 1999
PMS2	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	De Rosa *et al.*, 2000
TGFRBR2	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Lu *et al.*, 1998
EXO1	Hereditary Non-Polyposis Colorectal Cancer	colorectum, endometrium	Wu *et al.*, 2001
APC	Familial Adenomatous Polyposis	colon	Zając *et al.*, 2000
p53, CHK2	Li-Fraumeni syndrome	sarcoma, leukemia, suprarenal gland, breast	Bell *et al.*, 1999; Sullivan *et al.*, 2002
VHL	von Hippel Lindau	hemangioblastoma of the brain, eye and renal	Cybulski *et al.*, 1999; Hes *et al.*, 2000
Rb-1	Retinoblastoma	retinoblastoma	Jakubowska *et al.*, 2001b; Zajączek *et al.*, 1999
RET	Familial Medullary Thyroid Cancer	medullary thyroid	Menko *et al.*, 2002; Rey *et al.*, 2001
CDH1	Hereditary Diffuse Gastric Cancer	stomach	Salahshor *et al.*, 2001
SMAD4	Juvenile Polyposis	colon	Howe *et al.*, 1998; Kim *et al.*, 2000
PTEN	Cowden disease	breast, thyroid	De Vivo *et al.*, 2000
STK11	Peutz-Jegers syndrome	breast, pancreas	Westerman *et al.*, 1999; Yoon *et al.*, 2000

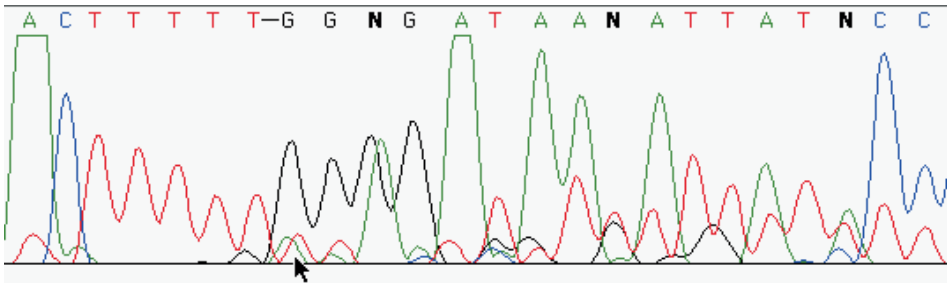
reached about 50, there is still a large proportion of strong tumor aggregations without known molecular defects. For example:

a) Since 2001 we performed the first worldwide population screening for familial cancers in West-Pomerania. During the first year of this programme we performed a complete diagnostic process including pedigree analysis, DNA testing and clinical examination of about 400 000 individuals. About 2600 families with at least three first degree relatives affected by tumors, thus showing the most characteristic feature of monogenic dominant genetic disorders, have been identified, but constitutional mutations were detected in only about 5% of them (Lubiński *et al.*, 2002).

b) We performed sequencing in 200 families with at least three cases of breast/ovarian cancers. Constitutional mutations of the *BRCA1* gene were found in 63% (126/200) and of the *BRCA2* gene in 3% (6/200) of families. Most probably about 30% of cancer aggregations are caused by *BRCAX* gene/genes mutations. Large *BRCA1/BRCA2* deletions were found only in five cases (Górski *et al.*, 2002).

c) Sequencing of the *MSH2/MLH1* genes in families with Lynch syndrome diagnosed definitely or with high probability allowed us to detect constitutional mutations in about 34% of cases. We screened 101 HNPCC kindreds from Poland and Baltic States fulfilling the Amsterdam II diagnostic criteria (17/101) or suspected HNPCC criteria for mutations in *MSH2* and *MLH1* (84/101). Suspected HNPCC families were diagnosed if among first degree relatives of patient with colorectal cancer at least one cancer of the colon or

a)



b)

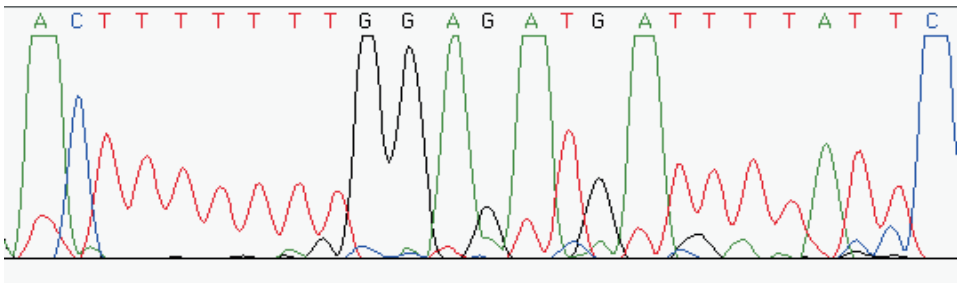


Figure 1. The first Polish *MSH6* mutation c.3311-3312 delTT.

Detection of a germline *MSH6* mutation by sequence analysis; arrow indicates the site of deletion; a) mutant; b) wilde type (Suchy *et al.*, 2002). Using of lower case "c" in front of the nucleotide number is recommended for cDNA by the Nomenclature Working Group (Antonarakis SE and the Nomenclature Working Group (1998) Recommendations for a Nomenclature System for Human Gene Mutations. *Hum Mutat.;* **11**: 1–3).

endometrium have been recognised and at least one of these tumors has been diagnosed under age of 50 (Kurzawski *et al.*, 2002a). Thus, again there is very high probability that in a significant proportion of families with strong aggregation of colorectal/ endometrial cancers the genes responsible for a major molecular defect are not known yet. We were able to show that one of such genes may be *MSH6*. The *MSH6* gene is one of the mismatch repair genes. Mutations in this gene, in opposite to *MSH2/MLH1* genes, are much rarer and exhibit distinct phenotype. In our *MSH6* family tumor spectrum include endometrioid ovarian cancer, colon cancer and two endometrial cancers. In patient, with previously excluded germline mutation in *MSH2/MLH1* genes, we identified in exon 5 of *MSH6* gene the frameshift mutation (Figs. 1 and 2) (Suchy *et al.*, 2002).

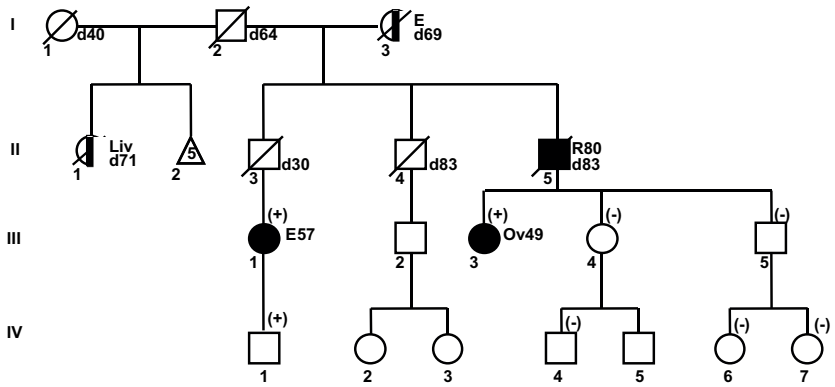


Figure 2. Pedigree of an *MSH6* family with c.3311-3312 delTT mutation.

E, endometrial cancer; R, rectal cancer; Ov, ovarian cancer; Liv, liver cancer; number after the abbreviation indicates the age at diagnosis; d, death age; (+), *MSH6* mutation positive; (-), *MSH6* mutation negative.

d) One of the genes recognized as a cause of stomach cancer familial aggregations is E-cadherin. We sequenced 53 patients with stomach cancers from families with clinical features of hereditary gastric tumors (at least three relatives affected by stomach cancer at any age or two relatives affected by stomach cancer with at least one diagnosed under age of 50) and in no case the E-cadherin constitutional mutations have been found (A. Jakubowska, unpublished data).

IDENTIFICATION OF MOLECULAR BASIS OF STRONG CANCER FAMILY AGGREGATIONS

Major work has still to be performed in order to identify molecular basis of strong cancer family aggregations. A promising methodology is linkage analysis with intragenic markers for candidate genes. It is reasonable to expect that for example for strong cancer aggregations with the involvement of breast cancer genes known to be connected with *BRCA1/BRCA2*, and for cancer aggregations with the involvement of colon cancer genes known for their aggregation with *MSH2/MLH1* should be considered (Tables 2–5, Fig. 3). Interactions between *BRCA1*, *BRCA2*, *MSH2* and *MLH1* and associated gene proteins have been recognised using different systems, mainly by immunoprecipitation and mass spectrometric analysis of associated proteins (Deng & Brodie, 2000; Wang *et al.*, 2000).

Table 2. *BRCA1* associated genes

Genes	References
BASC:*BRCA1*-ASSOCIATED GENOME SURVEILLANCE COMPLEX: *-RAD50-MRE11-NBS1,* *-ATM,* *-BLM,* *-MSH2-MSH6* HETERODIMER *-MLH1-PMS2* HETERODIMER *-MSH3,* *-REPLICATION FACTOR C*	Deng & Brodie, 2000; Futaki & Liu, 2001; Kerr & Ashworth, 2001; Wang *et al.*, 2000; Wang *et al.*, 2001a; Welcsh *et al.*, 2000; Yoshikawa *et al.*, 2000
RAD51	Kerr & Ashworth, 2001; Wang *et al.*, 2000; Wang *et al.*, 2001a; Welcsh *et al.*, 2000; Yoshikawa *et al.*, 2000
BACH1	Kerr & Ashworth, 2001
FANCD2	Futaki & Liu, 2001; Kerr & Ashworth, 2001
BARD1	Ghimenti *et al.*, 2002; Kerr & Ashworth, 2001; Wang *et al.*, 2001a; Welcsh *et al.*, 2000; Yoshikawa *et al.*, 2000
CtIP	Deng & Brodie, 2000; Kerr & Ashworth, 2001; Welcsh *et al.*, 2000
GADD45	Kerr & Ashworth, 2001
BRCA2	Deng & Brodie, 2000; Welcsh *et al.*, 2000
GADD153, Cyclin B1, P1N1, PCNA,zbrk1, p300, P/CAF(RNA Polymerase II holoenzyme), Ki-67, Bax, p21, STAT1, STAT3, JAK1, JAK2,	Kerr & Ashworth, 2001
BAP1	Welcsh *et al.*, 2000
RB	Deng & Brodie, 2000; Welcsh *et al.*, 2000
p53	Deng & Brodie, 2000; Welcsh *et al.*, 2000; Yoshikawa *et al.*, 2000
MYC	Deng & Brodie, 2000; Welcsh *et al.*, 2000
HDAC1, HDAC2	Deng & Brodie, 2000; Welcsh *et al.*, 2000
RHA	Deng & Brodie, 2000; Welcsh *et al.*, 2000
BRG1	Kerr & Ashworth, 2001
casein kinase	Deng & Brodie, 2000
E2F	Deng & Brodie, 2000

MODIFIERS

The cancer risk in *BRCA1, MSH2* and *MLH1* mutation carriers is at the level of about 50–80%. It has been shown recently that the risk heterogeneity may be related to modifying environmental and genetic factors (Table 6).

The results of studies on modifying features are not consistent. In our opinion this is caused by methodology problems: short series of cases studied, differences in ethnic origin and mutation types, the lack of matching for environmental features. Recently, we performed studies on the modifying effect of the polymorphic 135C→G *Rad51* allele on breast cancer risk in carriers of *BRCA1* 5382insC. Analyses on 83 pairs matched very carefully for reproductive factors allowed us to show more than 2x risk reduction in women with the 135C→G form of *Rad51*. This form has been found in 37% of the unaffected *BRCA1*

Table 3. *BRCA2*-associated genes

Genes	References
RAD51	Kerr & Ashworth, 2001; Welcsh *et al.*, 2000
p300, CtIP, P/CAF (RNA Polymerase II holoenzyme)	Kerr & Ashworth, 2001
BRAF35	Kerr & Ashworth, 2001
BRCA1	Welcsh *et al.*, 2000
BARD1	Ghimenti *et al.*, 2002
BCCIP	Liu *et al.*, 2001

Table 4. *MSH2*-associated genes

Genes	References
MSH3	Guerrette *et al.*, 1998; Peltomäki *et al.*, 2001
MSH6	Guerrette *et al.*, 1998; Peltomäki *et al.*, 2001
Exo1	Schmutte *et al.*, 2001
BRCA1	Wang *et al.*, 2001a
BARD1	Wang *et al.*, 2001a

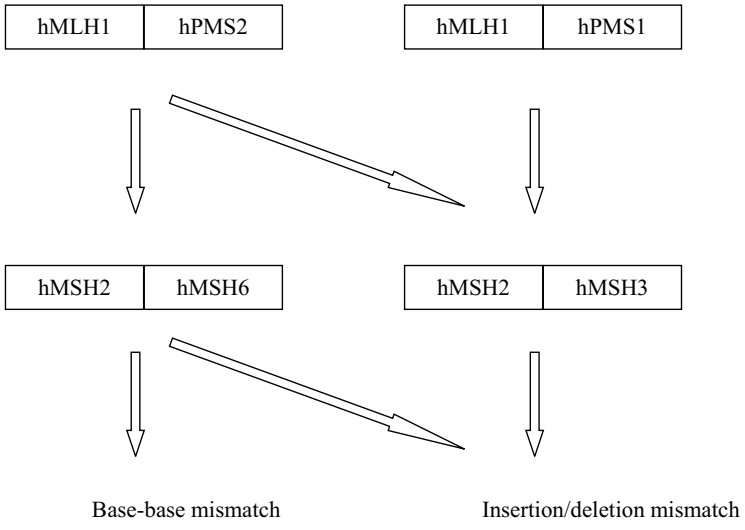


Figure 3. Interactions between mismatch repair genes.

The complex hMSH2–hMSH6 is responsible for the repair of base-base mismatches and base insertion/deletion mismatches, whilst the complex hMSH2–hMSH3 is only responsible for the repair of base insertion/deletion mismatches (Kolodner & Marsischky, 1999)

Table 5. *MLH1*-associated genes

Genes	References
PMS1	Schmutte *et al.*, 2001
PMS2	Guerrette *et al.*, 1999; Peltomäki *et al.*, 2001, Schmutte *et al.*, 2001; Yuan *et al.*, 2002
Exo1	Schmutte *et al.*, 2001

Table 6. Genes modifying cancer risk

Gene		Risk		References
Modified	Modifier	Increased	Decreased	
BRCA2	***Rad51*** *135C→G*	Breast cancer	Ovarian cancer	Levy-Lahad *et al.*, 2001; Wang *et al.*, 2001b
BRCA1/2	***ATM*** *T7271G* *IVS10-6T→G*	Breast cancer		Chenevix-Trench *et al.*, 2002; Maillet *et al.*, 2000; Teraoka *et al.*, 2001
MLH1/MSH2	*ATM* *1853N polymorphism vs. 1853D polymorphism*	Colorectal cancer and other HNPCC-related cancers		
BRCA1	***AR*** *≥28 CAG repeats*	Breast cancer		Rebbeck *et al.*, 1999
BRCA1 *BRCA2*	***AIB1*** *At least 28 or 29 polyglutamine repeats*	Breast cancer		Rebbeck *et al.*, 2001
MLH1/MSH2	***CCND1*** *alternatively spliced transcript "b" vs. transcipt "a"*	Lower age at onset of colon cancer		Bala & Peltomäki, 2001

carriers (31/83) and in 17% of the affected carriers (14/83) and in 26% among 189 healthy population controls (Jakubowska *et al.*, 2002).

CONCLUSIONS

The molecular basis of the genetic background for hereditary cancers has been discovered for a significant proportion of tumors. However, for the majority of hereditary cancers there is still lack of fundamental knowledge. Summarised results indicate directions of studies on identification of novel genes involved in pathogenesis of cancer family syndromes, which can be planned in the near future. It can be expected that in the near perspective of 5–10 years studies using existing registry data/material and the latest novel technology will allow the identification of the molecular background for the majority of hereditary cancers which will have enormous practical consequences especially for the prevention of malignancies.

REFERENCES:

Anderson TI, Wooster R, Laake K, Collins N, Warren W, Skrede M, Elles R, Tveit KM, Johnston SR, Dowsett M, Olsen AO, Moller P, Stratton MR, Borresen-Dale AL. (1997) Screening for ESR mutations in breast and ovarian cancer patients. *Hum Mutat.*; **9:** 531–6.

Bala S, Peltomäki P. (2001) CYCLIN D1 as a genetic modifier in hereditary nonpolyposis colorectal cancer. *Cancer Res.*; **61**: 6042–5.

Bell DW, Varley JM, Szydło TE, Kang DH, Wahrer DC, Shannon KE, Lubratovich M, Verselis SJ, Isselbacher KJ, Fraumeni JF, Birch JM, Li FP, Garber JE, Haber DA. (1999) Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. *Science.*; **286**: 2528–31.

Berends MJ, Wu Y, Sijmons RH, Mensink RG, van der Sluis T, Hordijk-Hos JM, de Vries EG, Hollema H, Karrenbeld A, Buys CH, van der Zee AG, Hofstra RM, Kleibeuker JH. (2002) Molecular and clinical characteristics of MSH6 variants: an analysis of 25 index carriers of a germline variant. *Am J Hum Genet.*; **70**: 26–37.

Broeks A, Urbanus JH, Floore AN, Dahler E, Klijn JG, Rutgers EJ, Devilee P, Russell NS, van Leeuwen FE, van't Veer LJ. (2000) ATM-heterozygous germline mutations contribute to breast cancer-susceptibility. *Am J Hum Genet.*; **66**: 494–500.

Chenevix-Trench G, Spurdle AB, Gatei M, Kelly H, Marsh A, Chen X, Donn K, Cummings M, Nyholt D, Jenkins MA, Scott C, Pupo GM, Dork T, Bendix R, Kirk J, Tucker K, McCredie MR, Hopper JL, Sambrook J, Mann GJ, Khanna KK. (2002) Dominant negative ATM mutations in breast cancer families. *J Natl Cancer Inst.;* **94**: 205–15.

Cybulski C, Krzystolik K, Lubiński J. (1999) Human gene mutations. Gene symbol: VHL. Disease: von Hippel-Lindau syndrome. *Hum Genet.*; **104:** 194.

Deng CX, Brodie SG. (2000) Roles of BRCA1 and its interacting proteins. *BioEssays.;* **22:** 728–37.

de los Rios P, Jack E, Kuperstein G, Lynch H, Lubiński J, Narod SA. (2001) Founder mutations of BRCA1 and BRCA2 in North American families of Polish origin that are affected with breast cancer. *Am J Hum Genet.;* **68:** 546.

De Vivo I, Gertig DM, Nagase S, Hankinson SE, O'Brien R, Speizer FE, Parsons R, Hunter DJ. (2000) Novel germline mutations in the PTEN tumour suppressor gene found in women with multiple cancers. *J Med Genet.*; **37:** 336–41.

De Rosa M, Fasano C, Panariello L, Scarano MI, Belli G, Iannelli A, Ciciliano F, Izzo P. (2000) Evidence for a recessive inheritance of Turcot's syndrome caused by compound heterozygous mutations within the PMS2 gene. *Oncogene.*; **19**: 1719–23.

Dębniak T, Górski B, Cybulski C, Jakubowska A, Kurzawski G, Kładny J, Lubiński J. (2001) Comparison of Alu-PCR, microsatellite instability and immunohistochemical analyses in finding features characteristic for hereditary nonpolyposis colorectal cancer. *J Cancer Res Clin Oncol.*; **127**: 565–9.

Futaki M, Liu JM. (2001) Chromosomal breakage syndromes and the BRCA1 genome surveillance complex. *Trends Mol Med.*; **7:** 560–5.

Ghimenti C, Sensi E, Presciuttini S, Brunetti IM, Conte P, Bevilacqua G, Caligo MA. (2002) Germline mutations of the BRCA1-associated ring domain (BARD1) gene in breast and breast/ovarian families negative for BRCA1 and BRCA2 alterations. *Genes Chromosomes Cancer.*; **33**: 235–42.

Górski B, Byrski T, Huzarski T, Jakubowska A, Menkiszak J, Gronwald J, Płużańska A, Bębenek M, Fischer-Maliszewska L, Grzybowska E, Narod SA, Lubiński J. (2000) Founder mutations in the BRCA1 gene in Polish families with breast-ovarian cancer. *Am J Hum Genet.;* **66:** 1963–8.

Górski B, Jakubowska A, Medrek K, Masojć B, Mierzejewski M, Byrski T, Huzarski T, Dębniak T, Cybulski C, Menkiszak J, Gronwald J, Tołoczko-Grabarek A, Zajączek S, Stawicka M , Mackiewicz A, Bębenek M, Fiszer-Maliszewska Ł, Grzybowska E, Haus O, Janiszewska H, Niepsuj S, Góźdź S, Zaremba L, Soroko D, Płużańska M, Kilar E , Czudowska D, Waśko B, Miturski R, Mielcarek, Urbański K, Koc J, Rozmiarek A, Lubiński J. (2002) BRCA1/BRCA2 mutation spectrum in Polish families with strong aggregation of breast/ovarian cancers. *Hereditary cancers – prophylactics, diagnostics, treatment. International Conference, Międzyzdroje, Poland, May 2002*: 36.

Guerrette S, Wilson T, Gradia S, Fishel R. (1998) Interactions of human hMSH2 with hMSH3 and hMSH2 with hMSH6: examination of mutations found in hereditary nonpolyposis colorectal cancer. *Mol Cell Biol.;* **18:** 6616–23.

Guerrette S, Acharya S, Fishel R. (1999) The interaction of the human MutL homologues in hereditary nonpolyposis colon cancer. *J Biol Chem.*; **274:** 6336–41.

Hes FJ, McKee S, Taphoorn MJ, Rehal P, van Der Luijt RB, McMahon R, van Der Smagt JJ, Dow D, Zewald RA, Whittaker J, Lips CJ, MacDonald F, Pearson PL, Maher ER. (2000) Cryptic von Hippel-Lindau disease: germline mutations in patients with haemangioblastoma only. *J Med Genet.*; **37**: 939–43.

Howe JR, Roth S, Ringold JC, Summers RW, Jarvinen HJ, Sistonen P, Tomlinson IP, Houlston RS, Bevan S, Mitros FA, Stone EM, Aaltonen LA. (1998) Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science.*; **280**: 1086–8.

Huang J, Kuismanen SA, Liu T, Chadwick RB, Johnson CK, Stevens MW, Richards SK, Meek JE, Gao X, Wright FA, Mecklin JP, Jarvinen HJ, Gronberg H, Bisgaard ML, Lindblom A, Peltomäki P. (2001) MSH6 and MSH3 are rarely involved in genetic predisposition to nonpolypotic colon cancer. *Cancer Res.*; **61**: 1619–23.

Jakubowska A, Górski B, Byrski T, Huzarski T, Gronwald J, Menkiszak J, Cybulski C, Dębniak T, Hadaczek P, Scott RJ, Lubiński J. (2001) Detection of germline mutations in the BRCA1 gene by RNA-based sequencing. *Hum Mutat.;* **18:** 149–56.

Jakubowska A, Górski B, Kurzawski G, Dębniak T, Hadaczek P, Cybulski C, Kładny J, Oszurek O, Scott RJ, Lubiński J. (2001) Optimization of experimental conditions for RNA-based sequencing of MLH1 and MSH2 genes. *Hum Mutat.;* **17**: 52–60.

Jakubowska A, Zajączek S, Haus O, Limon J, Kostyk E, Krzystolik Z, Lubiński J. (2001) Novel RB1 gene constitutional mutations found in Polish patients with familial and/or bilateral retinoblastoma. *Hum Mutat.*; **18:** 459.

Jakubowska A, Narod S, Goldgar D, Mierzejewski M, Masojć B, Nej K, Huzarska J, Byrski T, Górski B, Lubiński J. (2002) Breast cancer risk reduction associated with the *RAD51* polymorphism among carriers of the BRCA1 5382insC mutation in Poland. *CEBP.*; (in press).

Jensen DE, Proctor M, Marquis ST, Gardner HP, Ha SI, Chodosh LA, Ishov AM, Tommerup N, Vissing H, Sekido Y, Minna J, Borodovsky A, Schultz DC, Wilkinson KD, Maul GG, Barlev N, Berger SL, Prendergast GC, Rauscher FJ. (1998) 3rd. BAP1: a novel ubiquitin hydrolase which binds to the BRCA1 RING finger and enhances BRCA1-mediated cell growth suppression. *Oncogene.*; **16**: 1097–112.

Kerr P, Ashworth A. (2001) New complexities for BRCA1 and BRCA2. *Curr Biol.;* **11**: R668–76.

Kim IJ, Ku JL, Yoon KA, Heo SC, Jeong SY, Choi HS, Hong KH, Yang SK, Park JG. (2000) Germline mutations of the dpc4 gene in Korean juvenile polyposis patients. *Int J Cancer.;* **86**: 529–32.

Kolodner RD, Marsischky GT. (1999) Eukaryotic DNA mismatch repair. *Curr Opin Genet Dev.*; **9**: 89–96.

Kurzawski G, Kładny J, Dębniak T, Lubiński J. (1999) Gene symbol: MLH1. Disease: colorectal cancer, non-polyposis. *Hum Genet.;* **105:** 00–00.

Kurzawski G, Safranow K, Suchy J, Chlubek D, Scott RJ, Lubiński J. (2002) Mutation analysis of MLH1 and MSH2 genes performed by denaturing high-performance liquid chromatography. *J Biochem Biophys Methods.*; **51:** 89–100.

Kurzawski G, Suchy J, Kładny J, Safranow K, Jakubowska A, Elsakov P, Kucinskas V, Gardovski J, Irmejs A, Sibul H, Huzarski T, Byrski T, Dębniak T, Cybulski C, Gronwald J, Oszurek O, Clark J, Góźdź S, Niepsuj S, Słomski R, Pławski A, Łącka-Wojciechowska A, Rozmiarek A, Fiszer-Maliszewska Ł, Bębenek M, Sorokin D, Stawicka M, Godlewski D, Richter P, Brożek I, Wysocka B, Jawień A, Banaszkiewicz Z, Kowalczyk J, Czudowska D, Goretzki PE, Moeslein G, Lubiński J. (2002) Germline MSH2 and MLH1 mutational spectrum in HNPCC families from Poland and Baltic States. *J Med. Genet.*; (in press).

Levy-Lahad E, Lahad A, Eisenberg S, Dagan E, Paperna T, Kasinetz L, Catane R, Kaufman B, Beller U, Renbaum P, Gershoni-Baruch R. (2001) A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers. *Proc Natl Acad Sci U S A.*; **98**: 3232–6.

Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. (2000) Environmental and heritable factors in the causation of cancer — analyses of cohorts of twins from

Sweden, Denmark, and Finland. *N Eng J Med.;* **343:** 78–85.

Liu J, Yuan Y, Huan J, Shen Z. (2001) Inhibition of breast and brain cancer cell growth by BCCIPalpha, an evolutionarily conserved nuclear protein that interacts with BRCA2. *Oncogene.*; **20**: 336–45.

Lu SL, Kawabata M, Imamura T, Akiyama Y, Nomizu T, Miyazono K, Yuasa Y. (1998) HNPCC associated with germline mutation in the TGF-beta type II receptor gene. *Nat Genet.;* **19:** 17–8.

Lubiński J, Raczyński A, Tarhoni M, Blachowski M, Gronwald J, Huzarski T, Byrski T, Grabarek-Tołoczko A, Cybulski C, Kurzawski G, Jakubowska A. (2002) Population screening for cancer family syndromes in West-Pomeranian Region of Poland with 1,7 mln of inhabitants. *Int J Cancer* (Suppl).; **13**: 92.

Maillet P, Chappuis PO, Vaudan G, Dobbie Z, Muller H, Hutter P, Sappino AP. (2000) A polymorphism in the ATM gene modulates the penetrance of hereditary non-polyposis colorectal cancer. *Int J Cancer.*; **88**: 928–31.

McKean-Cowdin R, Kolonel LN, Press MF, Pike MC, Henderson BE. (2001) Germ-line HER-2 variant and breast cancer risk by stage of disease. *Cancer Res.;* **61**: 8393–4.

Menko FH, van der Luijt RB, de Valk IA, Toorians AW, Sepers JM, van Diest PJ, Lips CJ. (2002) Atypical MEN type 2B associated with two germline RET mutations on the same allele not involving codon 918. *J Clin Endocrinol Metab.;* **87:** 393–7.

Olschwang S. (1999) Germline mutation and genome instability. *Eur J Cancer Prev.;* Suppl 1, 33–7.

Park JG, Vasen HF, Park KJ, Peltomäki P, Ponz de Leon M, Rodriguez-Bigas MA, Lubiński J, Beck NE, Bisgaard ML, Miyaki M, Wijnen JT, Baba S, Lynch HT (1999) Suspected hereditary nonpolyposis colorectal cancer: International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) criteria and results of genetic diagnosis. *Dis Colon Rectum.*; **42**: 710–5.

Peltomäki P, Vasen HF, Bisgaard M, Buerstedde M, Friedl W, Grandjouan S, Hutter P, Kohonen-Corish M, Kolodner R, Kurzawski G, Lindblom A, Lynch HT, Piepoli A, Pons de Leon M, Radice P, Thibodeau S, Weber W, West S, Wijnen J. (1997) Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. *Gastroenterology.*; **113**: 1146–58.

Peltomäki P, Gao X, Mecklin JP. (2001) Genotype and phenotype in hereditary nonpolyposis colon cancer: a study of families with different vs. shared predisposing mutations. *Familial Cancer.;* **1**: 9–15.

Rebbeck TR, Kantoff PW, Krithivas K, Neuhausen S, Blackwood MA, Godwin AK, Daly MB, Narod SA, Garber JE, Lynch HT, Weber BL, Brown M. (1999) Modification of BRCA1-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat. *Am J Hum Genet.;* **64:** 1371–7.

Rebbeck TR, Wang Y, Kantoff PW, Krithivas K, Neuhausen SL, Godwin AK, Daly MB, Narod SA, Brunet JS, Vesprini D, Garber JE, Lynch HT, Weber BL, Brown M. (2001) Modification of BRCA1- and BRCA2-associated breast cancer risk by AIB1 genotype and reproductive history. *Cancer Res.*; **61**: 5420–4.

Rey JM, Brouillet JP, Fonteneau-Allaire J, Boneu A, Bastie D, Maudelonde T, Pujol P. (2001) Novel germline RET mutation segregating with papillary thyroid carcinomas. *Genes Chromosomes Cancer.*; **32**: 390–1.

Salahshor S, Hou H, Diep CB, Loukola A, Zhang H, Liu T, Chen J, Iselius L, Rubio C, Lothe RA, Aaltonen L, Sun XF, Lindmark G, Lindblom A. (2001) A germline E-cadherin mutation in a family with gastric and colon cancer. *Int J Mol Med.*; **8:** 439–43.

Schmutte C, Sadoff MM, Shim KS, Acharya S, Fishel R. (2001) The interaction of DNA mismatch repair proteins with human exonuclease I. *J Biol Chem.*; **276:** 33011–8.

Suchy J, Kurzawski G, Jakubowska A, Lubiński J. (2002) Ovarian cancer of endometrioid

type as a part of MSH6 gene mutation phenotype. *J Hum Genet.*; (in press).

Sullivan A, Yuille M, Repellin C, Reddy A, Reelfs O, Bell A, Dunne B, Gusterson BA, Osin P, Farrell PJ, Yulug I, Evans A, Ozcelik T, Gasco M, Crook T. (2002) Concomitant inactivation of p53 and Chk2 in breast cancer. *Oncogene.*; **21**: 1316–24.

Teraoka SN, Malone KE, Doody DR, Suter NM, Ostrander EA, Daling JR, Concannon P. (2001) Increased frequency of ATM mutations in breast carcinoma patients with early onset disease and positive family history. *Cancer.*; **92**: 479–87.

Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J. (2000) BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. *Genes Dev.;* **14:** 927–39.

Wang WW, Spurdle AB, Kolachana P, Bove B, Modan B, Ebbers SM, Suthers G, Tucker MA, Kaufman DJ, Doody MM, Tarone RE, Daly M, Levavi H, Pierce H, Chetrit A, Yechezkel GH, Chenevix-Trench G, Offit K, Godwin AK, Struewing JP. (2001) A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers. *Cancer Epidemiol Biomarkers Prev.*; **10**: 955–60.

Wang Q, Zhang H, Guerrette S, Chen J, Mazurek A, Wilson T, Slupianek A, Skórski T, Fishel R, Greene MI. (2001) Adenosine nucleotide modulates the physical interaction between hMSH2 and BRCA1. *Oncogene.*; **20**: 4640–9.

Welcsh PL, Owens KN, King MC. (2000) Insights into the functions of BRCA1 and BRCA2. *Trends Genet.*; **16**: 69–74.

Westerman AM, Entius MM, Boor PP, Koole R, de Baar E, Offerhaus GJ, Lubiński J, Lindhout D, Halley DJ, de Rooij FW, Wilson JH. (1999) Novel mutations in the LKB1/STK11 gene in Dutch Peutz-Jeghers families. *Hum Mutat.;* **13:** 476–81.

Wu Y, Berends MJ, Post JG, Mensink RG, Verlind E, Van Der Sluis T, Kempinga C, Sijmons RH, van der Zee AG, Hollema H, Kleibeuker JH, Buys CH, Hofstra RM. (2001) Germline mutations of EXO1 gene in patients with hereditary nonpolyposis colorectal cancer (HNPCC) and atypical HNPCC forms. *Gastroenterology.*; **120**: 1580–7.

Yoon K A, Ku JL, Choi HS, Heo SC, Jeong SY, Park YJ, Kim NK, Kim JC, Jung PM, Park JG. (2000) Germline mutations of the STK11 gene in Korean Peutz-Jeghers syndrome patients. *Br J Cancer.;* **82**: 1403–6.

Yoshikawa K, Ogawa T, Baer R, Hemmi H, Honda K, Yamauchi A, Inamoto T, Ko K, Yazumi S, Motoda H, Kodama H, Noguchi S, Gazdar AF, Yamaoka Y, Takahashi R. (2000) Abnormal expression of BRCA1 and BRCA1-interactive DNA-repair proteins in breast carcinomas. *Int J Cancer.*; **88**: 28–36.

Yuan ZQ, Gottlieb B, Beitel LK, Wong N, Gordon PH, Wang Q, Puisieux A, Foulkes WD, Trifiro M. (2002) Polymorphisms and HNPCC: PMS2-MLH1 protein interactions diminished by single nucleotide polymorphisms. *Hum Mutat.*; **19:** 108–13.

Zając V, Tomka M, Ilencikova D, Majek P, Stevurkova V, Kirchhoff T. (2000) A double germline mutations in the APC and p53 genes. *Neoplasma.*; **47:** 335–41.

Zajączek S, Jakubowska A, Górski B, Kurzawski G, Krzystolik Z, Lubiński J. (1999) Frequency and nature of germline Rb-1 gene mutations in a series of patients with sporadic unilateral retinoblastoma. *Eur J Cancer.*; **35**: 1824–7.