Breast Cancer Res Treat (2010) 123:315–320
DOI 10.1007/s10549-009-0634-4

PRECLINICAL STUDY

Association of rare *MSH6* variants with familial breast cancer

Marijke Wasielewski · Muhammad Riaz · Joyce Vermeulen · Ans van den Ouweland · Ineke Labrijn-Marks · Renske Olmer · Linda van der Spaa · Jan G. M. Klijn · Hanne Meijers-Heijboer · Dennis Dooijes · Mieke Schutte

Received: 8 September 2009 / Accepted: 2 November 2009 / Published online: 19 November 2009

Abstract Germline mutations in the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* predispose to Lynch syndrome (also known as hereditary non-polyposis colorectal cancer). Recently, we have shown that the *CHEK2* 1100delC mutation also is associated with Lynch syndrome/Lynch syndrome-associated families albeit in a polygenic setting. Two of the ten *CHEK2* 1100delC positive Lynch syndrome families additionally carried a pathogenic *MLH1* or *MSH6* mutation, suggesting that mutations in mismatch repair genes may be involved in *CHEK2* 1100delC-associated cancer phenotypes. A phenotype of importance is hereditary breast and colorectal cancer (HBCC), with the *CHEK2* 1100delC mutation present in almost one-fifth of the families—again in a polygenic setting. In order to evaluate the involvement of *MSH6* in polygenic CHEK2 cancer susceptibility, we, here, have analyzed the entire *MSH6* coding sequence for genetic alterations in 68 HBCC breast cancer families. Rare *MSH6* variants, with population frequencies below 1%, were identified in 11.8% of HBCC breast cancer families, whereas the same variants were identified in only 1.5% of population controls, suggesting that rare *MSH6* variants are associated with HBCC breast cancer ($P \leq 0.00001$). However, screening of the entire *MSH6* coding sequence in 68 non-HBCC breast cancer families showed a similar association (8.8 vs. ~1.4% in controls, $P \leq 0.001$), suggesting that rare *MSH6* variants are not confined to HBCC breast cancer. Together, our data suggest that rare *MSH6* variants may predispose to familial breast cancer. However, none of the rare *MSH6* variants are obviously pathogenic, suggesting that a more subtle disease mechanism may operate in breast carcinogenesis.

Keywords *CHEK2* 1100delC · Familial breast cancer · Hereditary breast and colorectal cancer · MSH6 · Polygenic cancer susceptibility

M. Wasielewski · M. Riaz · J. Vermeulen · J. G. M. Klijn · H. Meijers-Heijboer · M. Schutte (✉)
Department of Medical Oncology, Josephine Nefkens Institute Be414, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands
e-mail: a.schutte@erasmusmc.nl

A. van den Ouweland · I. Labrijn-Marks · R. Olmer · L. van der Spaa · H. Meijers-Heijboer · D. Dooijes
Department of Clinical Genetics, Josephine Nefkens Institute Be414, Erasmus University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands

Introduction

In 2002, we and others have identified the truncating *CHEK2* 1100delC mutation as the first moderate-risk breast cancer susceptibility allele, present in about 5% of Dutch breast cancer families [1, 2]. In addition, we have shown that the *CHEK2* 1100delC mutation was also present among Lynch syndrome/Lynch syndrome-associated families and was particularly prevalent among breast cancer families with a hereditary breast and colorectal cancer (HBCC) phenotype (4 and 18%, respectively) [3, 4]. However, in each of these instances, *CHEK2* 1100delC appeared to confer cancer risks in a polygenic setting.

The association of *CHEK2* 1100delC with colorectal cancer phenotypes suggested known colorectal cancer genes as likely candidates for polygenic CHEK2 cancer susceptibility [4]. Germline mutations in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* have been identified as the major causes for Lynch syndrome (previously also known as hereditary non-

polyposis colorectal cancer, HNPCC; [5–7]). Interestingly, in two of the ten *CHEK2* 1100delC-positive Lynch syndrome-associated families, we had also identified pathogenic mutations in *MHL1* or *MSH6* [4]. Concomitance of *CHEK2* and *MSH6* mutations had reportedly also been identified in a Finnish breast cancer family and in the colorectal cancer cell line HCT15 [8–11]. During repair of DNA damage, activated CHEK2 is known to signal BRCA1, which in turn acts as a scaffold protein for several DNA damage response proteins, including MSH6 [12–14]. The close functional relation of CHEK2 and MSH6, together with the observed concomitance of mutations in the two genes suggested that *MSH6* mutations may be involved in CHEK2 polygenic cancer susceptibility. This hypothesis was particular appealing for the HBCC phenotype as *CHEK2* 1100delC is prevalent among these families, whereas *MSH6* mutations are identified among Lynch syndrome families that also include breast cancer [3, 15–17]. Here, we therefore have screened the *MSH6* gene for genetic alterations in 68 HBCC and 68 non-HBCC breast cancer families.

Patients and methods

Breast cancer families and population controls

One hundred thirty-six breast cancer families were selected from 578 breast cancer families registered at the Rotterdam Family Cancer Clinic at Erasmus MC. Breast cancer families were classified as hereditary breast and colorectal cancer (HBCC) families ($n = 68$) or non-HBCC families ($n = 68$). All families included at least two-first or second-degree relatives (DGRs) with breast cancer of whom at least one was diagnosed before the age of 60 years. HBCC families additionally included at least one patient with breast and colorectal cancer *or* at least one patient with colorectal cancer diagnosed before the age of 50 years who is within second DGR of a breast cancer patient *or* at least two colorectal cancer patients of whom at least one is within second DGR of a breast cancer patient [3].

All breast cancer families were screened for germline mutations in the *BRCA1* and *BRCA2* genes and the *CHEK2* 1100delC mutation, identifying 26 *BRCA1* mutant families, 6 *BRCA2* mutant families, and 18 families with the *CHEK2* 1100delC mutation. Two families were double mutant for *BRCA1* and the *CHEK2* 1100delC mutation. As part of our matching procedure, mutant *BRCA1*, *BRCA2*, and *CHEK2* 1100delC families were equally divided over HBCC and non-HBCC families. Pathogenic germline mutations in the *MLH1* and *MSH2* genes were not identified in any of the 68 HBCC families. *MLH1* and *MSH2* mutation status had not been determined for the 68 non-HBCC families.

All breast cancer families originated from the south-western Netherlands and have consented to search for cancer susceptibility genes. The 166 control individuals were geographically matched to the familial breast cancer cases and included spouses of heterozygous carriers of cystic fibrosis gene mutations, ascertained through the department of Clinical Genetics at Erasmus MC. The medical ethical committee of Erasmus MC approved this study.

MSH6 mutation analysis

The mismatch repair gene *MSH6* (NM_000179.2) was screened for mutations in blood-derived DNA of the youngest diagnosed breast cancer case in the family (index case). The complete coding sequence of the *MSH6* gene, including intron/exon boundaries up to 25 bases in the intron, was amplified by standard PCR. Amplified fragments were subsequently analyzed for genetic alterations by denaturing gradient gel electrophoresis (DGGE) or by direct sequencing as described [17–19]. Unique sequence alterations were confirmed at least once by sequence analysis of an independently generated PCR product. Primer sequences and reaction conditions are available upon request.

Statistical analysis

The difference between the mutation frequency in breast cancer patients versus controls was analyzed using Fisher's Exact Test. *P* values of 0.05 or smaller were considered significant. All statistical analyses were performed with STATA statistical package, release 10 (STATA Corp, College Station, TX).

Results and discussion

Rare *MSH6* variants associate with HBCC breast cancer

We analyzed the entire *MSH6* coding sequence in 68 breast cancer families with hereditary breast and colorectal cancer (HBCC). Sequence analysis identified 25 different sequence alterations among 68 HBCC families, including 10 intronic and 15 exonic variants (Table 1). In order to evaluate the significance of the identified *MSH6* variants for HBCC, all variants were subsequently genotyped in 166 geographically matched controls. Rare variants, with population frequencies below 1%, represented 56% (14/25) of the *MSH6* variants and each of these were identified only once or twice among the HBCC cohort. Four of the 14 rare *MSH6* variants identified among HBCC families were also identified in the control cohort. Thus, although none of the

Table 1 *MSH6* mutation analysis among 68 HBCC and 68 non-HBCC breast cancer families

MSH6 gene sequence[a]	Predicted protein effect	Minor allele/Total tested alleles (%)							
		HBCC		Non-HBCC		All BRC		Controls	
Prevalent variants (>1%)									
c.260 + 22C > G	–	31/136	(22.8)	23/136	(16.9)	54/272	(19.9)	58/332	(17.5)
c.3438 + 14A > T	–	58/136	(42.6)	58/136	(42.6)	116/272	(42.6)	126/322	(39.1)
c.3557-4dupT	–	26/136	(19.1)	26/136	(19.1)	52/272	(19.1)	56/324	(17.3)
c.4002-10delT	–	35/136	(25.7)	39/136	(28.7)	74/272	(27.2)	2/328	(25.6)
c.4002-10dupT	–	14/136	(10.3)	16/136	(11.8)	30/272	(11.0)	41/312	(13.1)
c.116G > A	p.G39E	25/136	(18.4)	24/136	(17.6)	49/272	(18.0)	52/332	(15.7)
c.186C > A	p.=	31/136	(22.8)	23/136	(16.9)	54/272	(19.9)	58/332	(17.5)
c.276A > G	p.=	29/136	(21.3)	22/136	(16.2)	51/272	(18.9)	53/332	(16.0)
c.540T > C	p.=	42/136	(30.9)	39/136	(28.7)	81/272	(29.8)	95/332	(28.6)
c.642C > T	p.=	12/136	(8.8)	14/136	(10.3)	26/272	(9.6)	38/332	(11.4)
c.1286C > G	p.L396V	2/136	(1.5)	0/136	–	2/272	(0.7)	6/332	(1.8)
Rare variants (< 1%)									
Intronic (up to 25 bases)									
c.457 + 13A > G	–	1/136	(0.7)	0/136	–	1/272	(0.4)	1/332	(0.3)
c.3439-16C > T	–	2/136	(1.5)	0/136	–	2/272	(0.7)	0/306	–
c.3647-11T > G	–	0/136	–	1/136	(0.7)	1/272	(0.4)	0/254	–
c.4001 + 12_4001 + 15delACTA	–	2/136	(1.5)	1/136	(0.7)	3/272	(1.1)	2/328	(0.6)
c.4002-10delTT	–	1/136	(0.7)	0/136	–	1/272	(0.4)	0/312	–
c.4002-10delTTT	–	0/136	–	1/136	(0.7)	1/272	(0.4)	1/312	(0.3)
c.4002-10delTTTT	–	0/136	–	1/136	(0.7)	1/272	(0.4)	0/312	–
c.4002-10dupTTT	–	1/136	(0.7)	1/136	(0.7)	2/272	(0.7)	0/312	–
Exonic synonymous									
c.1053C > T	p.=	1/136	(0.7)	0/136	–	1/272	(0.4)	0/332	–
c.1164C > T	p.=	0/136	–	1/136	(0.7)	1/272	(0.4)	0/332	–
c.2272C > T	p.=	0/136	–	1/136	(0.7)	1/272	(0.4)	0/332	–
c.2775A > C	p.=	1/136	(0.7)	0/136	–	1/272	(0.4)	0/332	–
c.3246G > T	p.=	1/136	(0.7)	2/136	(1.5)	3/272	(1.1)	0/332	–
c.3306T > A	p.=	1/136	(0.7)	1/136	(0.7)	2/272	(0.7)	0/332	–
Exonic non-synonymous									
c.73G > T	p.A25S	1/136	(0.7)	1/136	(0.7)	2/272	(0.7)	1/332	(0.3)
c.751A > G	p.I251 V	1/136	(0.7)	0/136	–	1/272	(0.4)	0/332	–
c.1508C > G	p.S503C	1/136	(0.7)	0/136	–	1/272	(0.4)	1/332	(0.3)
c.2045C > T	p.S682F	1/136	(0.7)	0/136	–	1/272	(0.4)	0/332	–
c.2633T > C	p.V878A	1/136	(0.7)	0/136	–	1/272	(0.4)	0/332	–
c.4072_4075dupGATT	p.K1358fsX2[b]	0/136	–	1/136	(0.7)	1/272	(0.4)	0/332	–

Table 1 continued

Summary rare variants										
Minor allele/Total tested alleles (%)										
	All		Intronic		Exonic all		Exonic synonymous		Exonic non-synonymous	
HBCC families	16/136	(11.8)	7/136	(5.1)	9/136	(6.6)	4/136	(2.9)	5/136	(3.7)
Controls	5/306–332	(~1.5)	3/306–332	(~0.9)	2/332	(0.6)	0/332	(~0.0)	2/332–332	(0.6)
P value	<0.00001									
Non-HBCC families	12/136	(8.8)	5/136	(3.7)	7/136	(5.1)	5/136	(3.7)	2/136	(1.5)
Controls	4/254–332	(~1.4)	3/254–328	(~1.1)	1/332	(0.3)	0/332	(~0.0)	1/332	(0.3)
P value	<0.001									
All BRC families	28/272	(10.3)	12/272	(4.4)	16/272	(5.9)	9/272	(3.3)	7/272	(2.6)
Controls	6/254–332	(~2.1)	4/254–332	(~1.4)	2/332	(0.6)	0/332	(~0.0)	2/332	(0.6)
P value	<0.0001									

[a] Numbering of nucleotide changes according *MSH6* GenBank sequence NM_000179.2

[b] Frame shift mutation is indicated by the first changed codon and the number of newly encoded codons, including premature termination codon X This particular variant locates 3′ in the gene sequence predicting a protein shortened with only two amino acids. *BRC* breast cancer, *HBCC* hereditary breast and colorectal cancer

rare *MSH6* variants associated significantly with HBCC families, the combined frequency of the rare variants was significantly higher among HBCC families compared to controls (16/136 (11.8%) vs. 5/306–332 (~1.5%), $P < 0.00001$; Table 1). These results suggested that rare *MSH6* variants may predispose for HBCC breast cancer.

Rare *MSH6* variants associate with familial breast cancer

In order to evaluate if rare *MSH6* variants associate with HBCC breast cancer or rather with familial breast cancer in general, we also screened the entire *MSH6* coding sequence in 68 matched non-HBCC families (Table 1). Non-HBCC families were matched to the HBCC families with respect to their cancer pattern, i.e., the number of cancer patients per family, the number of cancer patients overall and the number of patients with single, double, triple, or more cancers (Table 2). In order to avoid selection for HBCC, the non-HBCC families have been counter selected for the presence of colorectal cancer. Six additional rare *MSH6* variants were identified among the non-HBCC families of which only one was also identified among the controls (Table 1). The combined frequency of rare *MSH6* variants was also significantly higher among non-HBCC families compared to controls (12/136 (8.8%) vs. 4/254–332 (~1.4%), $P < 0.001$; Table 1). Hence, the prevalence of rare *MSH6* variants among non-HBCC families is equally high as among HBCC families, indicating that rare *MSH6* variants are not only associated with HBCC breast cancer but also more likely with breast cancer in general. Combining the data on HBCC and non-HBCC families revealed a prevalence of rare *MSH6* variants of 10.3% among all breast cancer families, whereas the same variants were identified in approximately 2.1% of controls ($P < 0.0001$; Table 1), strongly suggesting that rare *MSH6* variants may predispose for familial breast cancer.

Do rare *MSH6* variants predispose for familial breast cancer?

Two aspects may question whether rare *MSH6* variants indeed predispose for familial breast cancer. First, we have not screened the entire *MSH6* coding sequence in the control cohort. Our strategy had been to genotype in the controls only those *MSH6* variants that had been identified among the familial breast cancer cohorts. Apart from the genotyped variant sequence, our primer design allowed analysis of the sequence surrounding the genotyped variant often including entire exon sequences and intron sequences up to 25 base pairs. In this way, we were able to analyze 75% of the *MSH6* coding sequence in all controls. In addition to the five rare *MSH6* variants that already had been identified in the breast cancer families, two variants (c.59C > T, p.A20 V and c.4002-10delCT) were once identified exclusively among the controls. Based on this low prevalence of rare *MSH6* variants that are exclusively present among the controls (2/254 (0.8%); Table 1), it may be anticipated that screening of the remaining quarter of the *MSH6* coding sequence in the controls is unlikely to identify many more rare *MSH6* variants.

Another aspect is that the underlying disease mechanism of how rare *MSH6* variants may predispose to breast cancer. We found that the prevalence of rare *MSH6* variants was

Table 2 Cancer incidence among 68 HBCC and 68 non-HBCC breast cancer families

	No. of cancer families		No. of cancers							
			BRC		CRC		Other cancers		Total cancers	
	HBCC	non-HBCC	HBCC	non-HBCC	HBCC	non-HBCC	HBCC	non-HBCC	HBCC	non-HBCC
Cancer families										
With three cancer cases	–	1	–	2	–	0	–	1	–	3
With four cancer cases	4	4	10	13	4	0	2	3	16	16
With five cancer cases	6	6	19	22	7	0	4	8	30	30
With six cancer cases	2	6	6	27	4	0	2	9	12	36
With seven cancer cases	4	9	17	41	6	1	5	21	28	63
With eight cancer cases	11	6	38	32	25	0	25	16	88	48
With nine cancer cases	10	8	37	45	18	2	35	25	90	72
With ten or more cancer cases	31	28	167	195	69	6	143	175	379	376
Total	68	68	294	377	133	9	216	258	643	644
Cancer cases	540	553								
With single tumors	451	473								
With double tumors	78	71								
With three or more tumors	11	9								

BRC breast cancer, *CRC* colorectal cancer, *HBCC* hereditary breast and colorectal cancer families; other cancer cases, cancer cases other than breast cancer or colorectal cancer

consistently higher among the breast cancer families than the controls, whether they were intronic or exonic and whether they were synonymous or non-synonymous. However, none of the identified rare *MSH6* variants are known pathogenic mutations. Evaluation of each of the rare *MSH6* variants with the splice prediction programs Berkeley Drosophila Genome Project (www.fruitfly.org/seq_tools/splice.html) and NetGene2 (www.cbs.dtu.dk./services/NetGene2/) did not predict structural effects. It thus remains unclear how these rare *MSH6* variants exert their putative oncogenic effect, particularly for the intronic variants and the non-synonymous exonic variants. However, are obvious pathogenic effects to be expected in a polygenic setting? Importantly, the statistical evidence from our analysis that rare *MSH6* variants associate with familial breast cancer is compelling ($P < 0.001$), strongly suggesting cancer predisposition by rare *MSH6* variants. Obviously, our analysis requires replication in independent familial breast cancer cohorts, and it also seems warranted to screen familial colorectal cancer cohorts, with particular focus to rare variants that are not obviously pathogenic. In this respect, our current findings are consistent with a report by Nevanlinna et al. in which 15 different *MSH6* variants were identified among 38 breast cancer families with colorectal cancer and/or endometrial cancer [20]. Three of the *MSH6* variants classified as rare variants, including two synonymous exonic variants and one intronic variant. The prevalence of rare *MSH6* variants in their familial breast cancer cohort is similar to the prevalence we report here ($3/38 = 7.9$ vs. 10.3% in our cohort) and supports our conclusion that rare *MSH6* variants are associated with familial breast cancer. Their and our observations both seem to point toward a currently unknown disease mechanism in breast carcinogenesis such as modulation of transcript expression levels or mediation of non-coding RNAs located in the genomic regions associated with these variants. Therefore, one may wonder whether this mechanism is similar to the as-yet unresolved disease mechanism underlying the more prevalent low-risk breast cancer alleles that recently have received much attention [21–26].

Acknowledgments We wish to thank all members of the breast cancer families that have participated in this study. Financial support was provided by the Dutch Cancer Society (DDHK 2003-2862) and the Susan G. Komen Breast Cancer Foundation (BCT R0601309). MR is funded by the Higher Education Commission (HEC) of the Government of Pakistan.

References

1. Meijers-Heijboer H, van den Ouweland A, Klijn J et al (2002) Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100-delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55–59. doi:10.1038/ng879
2. Vahteristo P, Bartkova J, Eerola H et al (2002) A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. Am J Hum Genet 71:432–438. doi:10.1086/341943
3. Meijers-Heijboer H, Wijnen J, Vasen H et al (2003) The CHEK2 1100delC mutation identifies families with a hereditary breast and colorectal cancer phenotype. Am J Hum Genet 72:1308–1314. doi:10.1086/375121

4. Wasielewski M, Vasen H, Wijnen J et al (2008) CHEK2 1100delC is a susceptibility allele for HNPCC-related colorectal cancer. Clin Cancer Res 14:4989–4994. doi:10.1158/1078-0432.CCR-08-0389
5. Jass JR (2006) Hereditary non-polyposis colorectal cancer: the rise and fall of a confusing term. World J Gastroenterol 12:4943–4950
6. Peltomaki P (2005) Lynch syndrome genes. Fam Cancer 4:227–232. doi:10.1007/s10689-004-7993-0
7. Vasen HF, Moslein G, Alonso A et al (2007) Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet 44:353–362. doi:10.1136/jmg.2007.048991
8. Bell DW, Varley JM, Szydlo TE et al (1999) Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome. Science 286:2528–2531. doi:10.1126/science.286.5449.2528
9. Lee SB, Kim SH, Bell DW et al (2001) Destabilization of CHK2 by a missense mutation associated with Li-Fraumeni Syndrome. Cancer Res 61:8062–8067
10. Papadopoulos N, Nicolaides NC, Liu B et al (1995) Mutations of GTBP in genetically unstable cells. Science 268:1915–1917. doi:10.1126/science.7604266
11. Vahteristo P, Tamminen A, Karvinen P et al (2001) p53, CHK2, and CHK1 genes in Finnish families with Li-Fraumeni syndrome: further evidence of CHK2 in inherited cancer predisposition. Cancer Res 61:5718–5722
12. Bartek J, Lukas J (2003) Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell 3:421–429. doi:10.1016/S1535-6108(03)00110-7
13. Lee JS, Collins KM, Brown AL, Lee CH, Chung JH (2000) hCds1-mediated phosphorylation of BRCA1 regulates the DNA damage response. Nature 404:201–204. doi:10.1038/35004614
14. 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 14:927–939. doi:10.1101/gad.14.8.927
15. Hendriks YM, Wagner A, Morreau H et al (2004) Cancer risk in hereditary nonpolyposis colorectal cancer due to MSH6 mutations: impact on counseling and surveillance. Gastroenterology 127:17–25. doi:10.1053/j.gastro.2004.03.068
16. Jensen UB, Sunde L, Timshel S et al (2009) Mismatch repair defective breast cancer in the hereditary nonpolyposis colorectal cancer syndrome. Breast Cancer Res Treat. doi:10.1007/s10549-009-0449-3
17. Wagner A, Hendriks Y, Meijers-Heijboer EJ et al (2001) Atypical HNPCC owing to MSH6 germline mutations: analysis of a large Dutch pedigree. J Med Genet 38:318–322. doi:10.1136/jmg.38.5.318
18. Ramsoekh D, Wagner A, van Leerdam ME et al (2008) A high incidence of MSH6 mutations in Amsterdam criteria II-negative families tested in a diagnostic setting. Gut 57:1539–1544. doi:10.1136/gut.2008.156695
19. Wasielewski M, Elstrodt F, Klijn JG, Berns EM, Schutte M (2006) Thirteen new p53 gene mutants identified among 41 human breast cancer cell lines. Breast Cancer Res Treat 99:97–101. doi:10.1007/s10549-006-9186-z
20. Vahteristo P, Ojala S, Tamminen A et al (2005) No MSH6 germline mutations in breast cancer families with colorectal and/or endometrial cancer. J Med Genet 42:e22. doi:10.1136/jmg.2004.022327
21. Easton DF, Pooley KA, Dunning AM et al (2007) Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 447:1087–1093. doi:10.1038/nature05887
22. Hunter DJ, Kraft P, Jacobs KB et al (2007) A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 39:870–874. doi:10.1038/ng2075
23. Stacey SN, Manolescu A, Sulem P et al (2007) Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 39:865–869. doi:10.1038/ng2064
24. Stacey SN, Manolescu A, Sulem P et al (2008) Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 40:703–706. doi:10.1038/ng.131
25. Ahmed S, Thomas G, Ghoussaini M et al (2009) Newly discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 41:585–590. doi:10.1038/ng.354
26. Zheng W, Long J, Gao YT et al (2009) Genome-wide association study identifies a new breast cancer susceptibility locus at 6q25.1. Nat Genet 41:324–328