Debate about TGFBR1 and the susceptibility to colorectal cancer

Laura Valle

Laura Valle, Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, 08908 Hospital de Llobregat, Spain

Author contributions: Valle L solely contributed to this paper.

Supported by The Spanish Ministry of Science and Innovation (Grant BFU2009-10281 and Ramón y Cajal contract) and the Scientific Foundation of Asociación Española Contra el Cáncer Correspondence to: Laura Valle, PhD, Hereditary Cancer Program, Catalan Institute of Oncology, IDIBELL, Av. Gran Vía 199-203, 08908 Hospital de Llobregat, Barcelona, Spain. lvalle@iconcologia.net

Telephone: +34-93-2607145 Fax: +34-93-2607466

Received: March 3, 2011 Revised: October 21, 2011

Accepted: October 28, 2011

Published online: January 15, 2012

Abstract

Recent years have witnessed enormous progress in our understanding of the genetic predisposition to colorectal cancer (CRC). Estimates suggest that all or most genetic susceptibility mechanisms proposed so far, ranging from high-penetrance genes to low-risk alleles, account for about 60% of the population-attributable fraction of CRC predisposition. In this context, there is increasing interest in the gene encoding the transforming growth factor β receptor 1 (TGFBR1); first when over a decade ago a common polymorphism in exon 1 (rs11466445, TGFBR1*6A/9A) was suggested to be a risk allele for CRC, then when linkage studies identified the chromosomal region where the gene is located as susceptibility locus for familial CRC, and more recently when allele-specific expression (ASE) of the gene was proposed as a risk factor for CRC. Published data on the association of TGFBR1 with CRC, regarding polymorphisms and ASE and including sporadic and familial forms of the disease, are often contradictory. This review gives a general overview of the most relevant studies in order to clarify the role of TGFBR1 in the field of CRC genetic susceptibility.

© 2012 Baishideng. All rights reserved.

Key words: Transforming growth factor β receptor 1; Transforming growth factor β receptor 1*6A; 9q linkage peak; Allele-specific expression; Colorectal cancer risk

Peer reviewers: Runjan Chetty, Professor, Department of Pathology and Gene Regulation, University of Glasgow, Western Infirmary (Pathology), Dumbarton Road, Glasgow, G11 6NT, Scotland, United Kingdom; Ke-Bin Liu, Assistant Professor, Department of Biochemistry and Molecular Biology, School of Medicine, Medical College of Georgia, Augusta, GA 30912, United States

Valle L. Debate about TGFBR1 and the susceptibility to colorectal cancer. World J Gastrointest Oncol 2012; 4(1): 1-8 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i1/1.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i1.1

GENETICS OF COLORECTAL CANCER

The estimated annual worldwide incidence of colorectal cancer (CRC) is 1 235 108, with a mortality rate of 609 051[1]. Lynch syndrome, the most common CRC syndrome formerly also known as hereditary non-polyposis CRC, accounts for approximately 3% of all CRC cases, while Familial Adenomatous Polyposis syndrome occurs in about 0.01% of the population, as well as other rarer polyposis syndromes, such as MYH-adenomatous polyposis, hereditary mixed polyposis, juvenile polyposis or Peutz-Jeghers syndromes among others[2,3]. All the above mentioned syndromes show high penetrance with respect to CRC risk; however, collectively they account for at most 3%-6% of all CRCs. Based on crude estimates of familial CRC, defined by the presence of two or more first-degree relatives affected with CRC, it is thought to involve approximately 20% of all CRCs[4,5]. In all, both case-control and twin studies indicate that hereditary factors contribute considerably to CRC[6].

Because of the complexity regarding the etiology of CRC that includes environmental as well as genetic fac-
tors, we now know that genetic susceptibility to CRC underlies an unknown proportion of both familial and sporadic cases. Therefore, the distinction between sporadic and familial cases of CRC is less dramatic than it has been classically considered. In fact, it has been thought for some time that a large fraction of familial and a majority of sporadic CRCs are likely to be due to low-penetrance alleles. Genome-wide association studies (GWAS) have identified a new repertoire of cancer susceptibility genes and loci characterized by high frequency of the risk allele and low relative risk, in line with the common disease-common variant paradigm[7-12]. There has been some enthusiasm in using combinations of low-risk alleles in individual risk assessment. However, even in combination, low-risk alleles tend to minimally improve the predictive power of the existing risk factors, such as family history. Recently, it was estimated that all or most genetic susceptibility mechanisms proposed so far account for about 60% of the population-attributable fraction of CRC predisposition[13], leaving approximately 40% of the genetic predisposition unexplained.

Moderate-penetrance genes are now thought to play a very important role in the already unexplained CRC susceptibility. However, until recently, important technical difficulties have prevented researchers from identifying these variants. These variants are rare, which may cause the inability of GWAS to detect them, and the risks conferred by them too low to be detected by linkage studies, the classical tool to identify high-penetrance disease genes. Hopefully, current whole-exome or -genome sequencing techniques will allow us to discover them.

Candidate gene approaches have sometimes been successful in identifying susceptibility variants. In this regard, considerable attention has been focused on the gene encoding the transforming growth factor β receptor 1 (TGFBR1).

**TRANSFORMING GROWTH FACTOR β PATHWAY IN CRC**

The transforming growth factor β (TGF-β) pathway is an important modulator of several biological processes, including cell proliferation, differentiation, migration and apoptosis[14]. The signaling pathway of TGF-β1, the most abundant form of TGF-β, plays an important role in carcinogenesis, having both tumor-suppressing and promoting activities. In normal and premalignant cells, TGF-β enforces homeostasis and suppresses tumor progression directly through cell-autonomous tumor-suppressive effects (cytostasis, differentiation, apoptosis) or indirectly through effects on the stroma (suppression of inflammation and stroma-derived mitogens). However, when cancer cells lose TGF-β tumor-suppressive response, they can use TGF-β to their advantage to initiate immune evasion, growth factor production, differentiation into an invasive phenotype and metastatic dissemination, or to establish and expand metastatic colonies[21,22].

Briefly, TGF-β binds to the cell surface receptor transforming growth factor β receptor 2 (TGFBR2), which results in their binding to and phosphorylation of TGFBR1. Subsequently, SMADs are phosphorylated by activated TGFBR1 and translocated into the nucleus, where they regulate transcription of their target genes[24,16,17].

The TGF-β and bone morphogenetic protein (BMP) pathways play an important role in the pathogenesis of CRC and other intestinal tumors. Inactivating somatic mutations in TGFBR2 occur in CRCs with microsatellite instability[18,19]. Whether TGFBR2 mutations have a causative role in colorectal carcinogenesis or whether they arise as a consequence of the hypermutable phenotype observed in cells with defective mismatch repair machinery is still a topic of debate. Mutations in TGFBR1 have been identified in CRC cell lines but are uncommon[20]. TGFBR1*6A/9A (rs11466445) is a common polymorphism in exon 1 of the gene that results in the deletion of three alanines from a stretch of nine alanines. Functional studies have suggested that TGFBR1*6A responds less well than the TGFBR1*9A allele to growth inhibitory signals of TGF-β. Moreover, it has been shown that TGFBR1*6A is somatically acquired in CRC and further analyses suggested that this somatic acquisition is a critical event in the early stages of cancer development, occurring both in epithelial and stromal cells during colorectal carcinogenesis[21,22]. SMAD2 and SMAD4 both map to chromosome 18q, a region commonly deleted in colon adenocarcinomas[19]. SMAD4 is mutated in 10%-38% of CRCs[25-27] and SMAD2 in 6%-8%[27,28]. SMAD3 mutations seem to be infrequent in tumors. BMP members belong to the TGF-β superfamily of proteins and the BMP pathway is inactivated in up to 70% of CRCs[29].

From the germline point of view, mutations in SMAD4 and BMPR1-A cause juvenile polyposis, a CRC susceptibility syndrome[29-31], and GWAS have identified low penetrance susceptibility alleles in the BMP pathway and SMAD[32,33]. TGFBR1 risk alleles will be discussed in the following section.

**TGFBR1 POLYMORPHIC VARIANTS AND CRC RISK**

TGFBR1*6A/9A (rs11466445) was identified in 1998 by Pasche et al[32]. From that moment on, it was considered a potential tumor susceptibility allele that has been associated with an increased incidence of several types of tumors, including CRC. Overall, however, for a long time the results were inconclusive and mixed, partially because small cohorts had been studied[31-33]. In order to overcome this problem, meta-analyses considering increasing number of studies have been published in the last years[35-38].

One of the most recent meta-analysis included 32 studies (9 for CRC) from different countries and types of tumors and comprised a total of 13662 cancer cases and 14147 controls, 2833 and 4255 respectively for CRC[39]. The results showed significantly higher overall cancer risk associated with TGFBR1*6A in all genetic models.
(for allelic effect: OR = 1.11, 95% CI: 1.03-1.21). However, when the analysis was subdivided by cancer type, significant associations were found in breast (for allelic effect: OR = 1.16, 95% CI: 1.01-1.34) and ovarian (for allelic effect: OR = 1.24, 95% CI: 1.00-1.54) cancers, but not in colorectal, bladder and prostate tumors. While for bladder and prostate cancers results were clearly non-significant, for CRC slightly borderline non-significance was found (for allelic effect: OR = 1.16, 95% CI: 0.94-1.42).

A subsequent meta-analysis based on 14 subgroup CRC case-control studies found that the heterozygote form 6A/9A showed a 12% increase of CRC risk compared to 9A/9A (OR = 1.12, 95% CI: 1.02-1.23), although no association was found for 6A/6A homozygotes[60].

In addition to TGFBR1*6A, another polymorphic variant, Int7G24A (rs334354), has also been implicated in cancer susceptibility, associations with kidney, bladder, invasive breast and non-small cell lung carcinomas, and osteosarcoma being reported[65,66,67]. When analyzed in CRC case-control cohorts, contradictory results have been obtained[64,65].

Due to the previous conflicting results published on TGFBR1 variants, especially TGFBR1*6A, Carvajal-Carmona et al[60] carried out a thorough assessment of TGFBR1 polymorphisms in relation to CRC risk in three series of CRC cases (n = 3101) and controls (n = 3334) of northern European ancestry. They found no association between CRC and TGFBR1*6A, not even when they considered interaction with other candidate variants in CRC genes that map close to the TGF-β/BMP pathway genes GREM1, BMP2, BMP4 and SMAD7. They also performed a comprehensive evaluation of common and rarer variants (n = 102) within the 75 kb haplotype block containing TGFBR1 and concluded that common variation at the TGFBR1 locus is unlikely to be associated with CRC risk. The lack of association persisted when long-range regulation was assessed by extending the analysis 500 kb on each side of the TGFBR1 haplotype block or by analyzing haplotypes instead of alleles.

Abulí et al[61] recently screened 7 polymorphic TGFBR1 variants with potential pathogenic effect, including TGFBR1*6A, in 515 CRC cases and 515 controls. Their results showed borderline significant association for TGFBR1*6A (unadjusted P = 0.049, dominant inheritance), but did not reach significance after multiple testing correction. No evidence of association with CRC risk was found for the other six TGFBR1 variants analyzed.

**ALLELE-SPECIFIC EXPRESSION OF TGFBR1**

Allele-specific expression (ASE), meaning that one allele is less or more expressed than the other, is now considered a mutational mechanism with phenotypic consequences and has been associated with increased cancer risk in some instances[68,69].

Studies in mice point to the relevance of haploinsufficiency of TGFBR1 in colorectal tumorigenesis. While the homozygous loss of Tgfr1 in mice (Tgfr1−/−) is lethal, the heterozygous loss (Tgfr1+/−) causes no obvious phenotypic traits. However, when Tgfr1+/− mice were bred into mice heterozygous for the ApcMin mutation, the double mutants acquired approximately a 2-fold increase in the number of intestinal adenomas in comparison with the ApcMin/+ mice, as well as colonic carcinomas, suggesting that haploinsufficiency for Tgfr1 predisposes to CRC[70,71].

Given the previous existing evidence, we studied ASE of TGFBR1 in unaffected tissue (blood) of CRC patients and controls using the SNaPshot technology and found that the reduced expression of one allele was a quantitative trait that was more common in patients (10%-20%) than in controls (1%-3%), conferring a substantially increased risk of CRC (OR = 8.7, 95% CI: 2.6-29.1). We also assessed the effect of ASE on the TGF-β pathway observing a subtle reduction of the SMAD-mediated signaling. Two major TGFBR1 haplotypes were predominant among the ASE cases; however, the causative genetic cause was not identified[72]. Given the potential use of ASE of TGFBR1 in the clinical evaluation of CRC risk, additional studies were consequently published[73,74,75,76].

Table 1 shows a summary of the studies published to date.

Although the balance is level regarding the number of studies that found more ASE in cases and controls, or no differences between both groups, several characteristics that may tip the balance should be considered: On the one hand, when trying to assess the robustness and reproducibility of the two standard methodologies to measure ASE, SNaPshot and pyrosequencing, it was found that, in contrast to pyrosequencing, SNaPshot yields high variability among different SNP markers, being highly dependent on RNA quality to obtain reliable and consistent results[73,74,75,76]. Recently Abadie et al[77] reported a study where exactly the same methodological approach as the original study[73] had been used, finding no differences between cases and controls. In that instance, high quality RNA was ensured by the careful and standardized procedure of blood collection and sample processing carried out, thus guaranteeing consistent results even when SNaPshot was used to measure ASE[77]. On the other hand, it seems that ASE might be more common among individuals who carry minor alleles for specific TGFBR1 SNPs. Therefore ASE could result more or less frequently, depending on the SNP markers used to define informative individuals. Another source of variability among studies might be the different unaffected tissues from which nucleic acids for ASE determination were extracted. Although we observed no differences in ASE frequencies when studying two different groups of CRC patients with different sources (uncultured) of nucleic acids[75], the fact that different types of tissues from the same individuals have never been analyzed still leaves a certain degree of uncertainty.

In all, the most recent results suggest that ASE differences between cases and controls are too subtle, if not nonexistent, to be used to assess CRC risk[73,74,75,76].
Table 1  Main characteristics of the studies published on allele-specific expression of transforming growth factor β receptor 1 and colorectal cancer risk

| Study                  | Majority population | Sample                      | Method         | Allelic markers | Informative cases/controls | ASE (binary) cases/controls | ASE higher in CRC cases |
|------------------------|---------------------|-----------------------------|----------------|----------------|--------------------------|---------------------------|------------------------|
| Valle et al[7] 2008    | Caucasian           | Blood                       | SNaPshot       | rs334348       | 138/105                  | 21.0%/2.9%                | Yes                    |
|                        |                     |                             |                | rs7871490      |                          |                           |                        |
|                        |                     |                             |                | rs334349       |                          |                           |                        |
|                        |                     |                             | Pyroseq        | rs1590         |                          |                           |                        |
|                        |                     |                             | SNaPshot       | rs8688         |                          |                           |                        |
|                        |                     |                             |                | rs334348       |                          |                           |                        |
|                        |                     |                             |                | rs334349       |                          |                           |                        |
|                        |                     |                             |                | rs420549       |                          |                           |                        |
| Guda et al[76] 2009    | Caucasian           | Lymph. cell line Normal colon | Pyroseq        | 46/17          | Familial:  | 4.3%/0%                   | No                      |
|                        |                     |                             |                | 98            | Sporadic: 44/0          |                           |                        |
| Carvajal-Carmena et al[74] 2010 | Caucasian | Lymph. cell line | Genescan | 6A/9A       | rs1590          | 29.2%/26.7%               | No                      |
| Pasche et al[77] 2010  | Caucasian           | Lymph. cell line            | Pyroseq        | 74/0           | Familial:  | 14.9%/-                   | Yes                    |
| Tomsic et al[78] 2010  | Caucasian           | Blood                       | Pyroseq        | 109/125        | Familial:  | 1.8%/1.6%                 | No                      |
|                        |                     |                             |                | 46.8%/31.2%    |                           |                           |                        |
| Segui et al[79] 2011   | Caucasian           | Normal colon                | Pyroseq        | 171/90         | Familial:  | 0%/2.2%                  | No                      |
| Abadie et al[80] 2011  | Caucasian           | Lymphocytes                 | Pyroseq        | 69/98          | Familial:  | 0%/0%                    | No                      |

Lymph. cell line: EBV transformed lymphoblastoid cell line; Pyroseq: Pyrosequencing; Binary: Allele-specific expression (ASE) was considered as a binary trait (ASE vs non-ASE); Continuous: ASE was considered as a continuous/quantitative trait. 49 cases were the same as in Valle et al[7], 2008. Cut-off values calculations based on own results: Valle et al[7] 2008 and Tomsic et al[78] 2010, ROC analysis; Segui et al[79] 2011 median controls ± 2 SD; Applied the cutoff values established by Valle et al[7] 2008.

As clearly pointed out by several authors, the real extent of ASE of TGFBR1 will probably only be known when technological and conceptual advances allow greater precision and circumvent the need of naturally occurring transcribed SNPs to differentiate the two alleles. With the current technologies and depending on the population studied, ASE can only be assessed in 25%-60% of all individuals, leaving open the possibility that ASE occurs, or does not occur, preferentially in those individuals uninformative for the allelic markers analyzed.

**TGFBR1 IN FAMILIAL CRC**

**Linkage to 9q22 in familial CRC**

The TGFBR1 gene co-localizes to the chromosomal region 9q22.2-31.2, first identified in 2003 as a putative susceptibility locus for colorectal neoplasia by Wiesner and colleagues using data from both discordant and concordant sibling pairs from 53 families[74,83]. This was later validated in studies from Sweden and the United Kingdom[80,83] and the locus designated as Colorectal Cancer Susceptibility 1 (CRCS1; MIM608812). It was estimated that it accounted for approximately 35% of the inherited susceptibility to CRC. Very recently, Wiesner and co-workers validated the original results in an independent sample (256 sibling pairs belonging to 110 families, 179 and 50 of them, respectively, from the original study) where the evidence of linkage to this region increased and the linkage on 9q22-31 was narrowed from 13.5 to 7.7 cm[83].

Other genome-wide linkage studies have failed to detect the 9q locus and it seems the underlying complexity of the 9q region and the differences in study design could explain the contradictory results[84]. Evidence suggests that the disease locus housed on 9q is specific to a familial syndrome with a phenotype of young age of onset and/or severity of the colorectal neoplasia[80,83].

**TGFBR1*6A in familial CRC**

Given the previous reports suggesting that TGFBR1*6A was a CRC susceptibility allele in the general population, in 2005 Pasche and co-workers hypothesized that this allele might explain a proportion of CRC patients with family histories meeting the Amsterdam criteria but without an identifiable mutation in a MMR gene, the so called familial CRC of type X (fCRC-X). In their series, TGFBR1*6A homozygotes were 13-fold times more frequent among fCRC-X patients (n = 64) than in the general population[85]. Other studies unsuccessfully tried to replicate the original results in larger series of fCRC-X patients[86], or of familial CRC selected based on more...
A塞 of TGFBR1 in familial CRC

When ASE of TGFBR1 was first described as a putative CRC susceptibility genetic trait, increasing interest was generated about its role in familial CRC. Already in the original study, familial cases were over-represented. Although the proportion of ASE was slightly higher among familial (25%) than non-familial cases (17%), the difference was not statistically significant. Guda et al. studied ASE in 46 informative familial cases, 31 of which (derived from 22 families) had previously shown linkage to 9q22. They detected ASE in two individuals, both from different families belonging to the 9q22 kinked cohort. Carvajal-Carmona et al. assessed ASE in 46 informative familial CRC patients from the CORGI cohort and did not find higher ASE in cases compared with controls. Likewise, Abadie et al., who included familial history and early-onset diagnosis of CRC as criteria for patients’ selection, did not find increased ASE in cases than in controls.

CONCLUSION

Researchers were very enthusiastic when TGFBR1*6A was first proposed as a putative CRC susceptibility allele, both for CRC in the general population and for familial CRC. However, the information obtained from larger series, meta-analyses and comprehensive studies including genetic variation in the whole TGFBR1 gene and large flanking regions suggest that the role of this allele in CRC predisposition is, at best, very subtle. A similar scenario is found regarding ASE of TGFBR1 related to CRC susceptibility. In this case, methodological improvements are key to perform an accurate assessment of ASE. The development of new technological advances that allow the measurement of ASE in a more precise and informative manner will provide the definitive answer to what the real extent of ASE of TGFBR1 in CRC patients is.

ACKNOWLEDGMENTS

Valle L thanks Gabriel Capellá and Victor Moreno for helpful discussions and critical review.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon: France: International Agency for Research on Cancer, 2010. Available from: URL: http://globocan.iarc.fr
2. Lynch HT, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 2009; 76: 1-18
3. Sweet K, Willis J, Zhou XP, Gallione C, Sawada T, Alhoppuro P, Khoo SK, Patocs A, Martin C, Bridgeman S, Heinz J, Pilarski R, Lehtonen R, Prior TW, Frebourg T, Teh BT, Marchuk DA, Aaltonen LA, Eng C. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. JAMA 2005; 294: 2465-2473
4. Aaltonen L, Johns L, Järvinen H, Mecklin JP, Houlston R. Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors. Clin Cancer Res 2007; 13: 356-361
5. Abdel-Rahman WM, Peltomäki P. Lynch syndrome and related familial colorectal cancers. Crit Rev Oncog 2008; 14: 1-22, discussion 23-31
6. de la Chapelle A. Genetic predisposition to colorectal cancer. Nat Rev Cancer 2004; 4: 769-780
7. Zanke BW, Greenwood CM, Rangrej J, Kustra R, Tenesa A, Farrington SM, Prendergast J, Olschewski S, Chiang T, Crowdy E, Ferretti V, Laflamme P, Sundararajan S, Roumy S, Ollivier JF, Robidoux F, Sladek R, Montpetit A, Campbell P, Bezieau S, O’Shea AM, Zogopoulou C, Cotterchio M, Newcomb P, McLaughlin J, Younghusband B, Green R, Green J, Porteous ME, Campbell H, Blanche H, Sahbatou M, Tabucher E, Bonaiti-Pellie C, Baecher B, Riboli E, Kury S, Chanock SJ, Potter J, Thomas G, Gallinger S, Hudson TJ, Dunlop MG. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. Nat Genet 2007; 39: 989-994
8. Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, Penegar S, Chandler I, Gorman M, Wood W, Barclay E, Lubbe S, Martin L, Sellick G, Jaeger E, Hubner R, Wild R, Rowan A, Fielding S, Howarth K, Silver A, Atkin W, Muir K, Logan R, Kerr D, Johnstone E, Sieber O, Gray R, Thomas H, Peto J, Cazier JB, Houlston R. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 2007; 39: 984-988
9. Broderick P, Carvajal-Carmona L, Pittman AM, Webb E, Howarth K, Rowan A, Lubbe S, Spain S, Sullivan K, Fielding S, Jaeger E, Vijayakrishnan J, Kemp Z, Gorman M, Chandler I, Papaemmanuil E, Penegar S, Wood W, Sellick G, Qureshi M, Teixeira A, Domingo E, Barclay E, Martin L, Sieber O, Kerr D, Gray R, Peto J, Cazier JB, Tomlinson I, Houlston RS. A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. Nat Genet 2007; 39: 1315-1317
10. Tomlinson IP, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, Spain S, Lubbe S, Walther A, Sullivan K, Jaeger E, Fielding S, Rowan A, Vijayakrishnan J, Domingo E, Chandler I, Kemp Z, Qureshi M, Farrington SM, Tenesa A, Prendergast JG, Barnetson RA, Penegar S, Barclay E, Wood W, Martin L, Gorman M, Thomas H, Peto J, Bishop DT, Gray R, Maher ER, Lucassen A, Kerr D, Evans DG, Schafmayer C, Buch S, Völzke H, Hampe J, Schreiber S, John U, Koessler T, Pharoah P, van Wezel T, Morreau H, Wijnen JT, Hopper JL, Southey MC, Giles GG, Severi G, Castelli-Bel S, Ruiz-Ponte C, Carroccio A, Castells A, Försti A, Hemminki K, Vodicka P, McLaughlin J, Smith JW, Agúndez JA, Ladero JM, de la Hoya M, Caldés T, Niittymäki I, Tuupanen S, Karhu A, Alaponten L, Cazier JB, Campbell H, Dunlop MG, Houlston RS. A genome-wide association study identifies common alleles of SMAD7 influence colorectal cancer risk. Nat Genet 2007; 39: 1315-1317
11. Tenesa A, Farrington SM, Prendergast JG, Porteous ME, Walker M, Haq N, Barnetson RA, Theodoratou E, Cetnarskyj R, Cartwright N, Semple C, Clark AJ, Reid FJ, Smith LA, Kaoussanakis K, Koessler T, Pharoah PD, Buch S, Schafmayer C, Tepel J, Schreiber S, Völzke H, Schmidt CO, Hampe J, Chang-Claude J, Hoffmeister M, Brenner H, Wilkening S, Canzian F, Capella G, Moreno V, Deary JJ, Starr JM, Tomlinson IP, Kemp Z, Howarth K, Carvajal-Carmona L, Webb E, Broderick P, Vijayakrishnan J, Houlston RS, Rennert G, Ball-
Suarez BK, Pal P, Jin CH, Kaushal R, Sun G, Jin L, Pasche B, Deka R, Catalona WJ. TGFBR1*6A is not associated with prostate cancer in men of European ancestry. *Prostate Cancer Prostatic Dis* 2005; 8: 50-53

Spillman MA, Schildkraut JM, Halabi S, Moorman P, Calingaert B, Bentley RC, Marks JR, Murphy S, Berchuck A. Transforming growth factor beta receptor I polyanaline repeat polymorphism does not increase ovarian cancer risk. *Gynecol Oncol* 2005; 97: 543-549

Kaklamani VG, Baddi L, Liu J, Rosman D, Phukan S, Bradley C, Hegarty C, McDaniel B, Rademaker A, Oddoux C, Ostrer H, Michel LS, Huang H, Chen Y, Ahsan H, Offit K, Pasche B. Combined genetic assessment of transforming growth factor-beta signaling pathway variants may predict breast cancer risk. *Cancer Res* 2005; 65: 3454-3461

Kaklamani V, Pasche B. Transforming Growth Factor Beta and breast cancer. *Cancer Treat Rev* 2005; 31: 129-156

Chen T, Jackson CR, Link A, Markey MP, Colligan BM, Douglass LE, Pemberton JD, Deddens JA, Graff JR, Carter JH. Int7G24A variant of transforming growth factor-beta receptor type I is associated with invasive breast cancer. *Clin Cancer Res* 2006; 12: 392-397

Feigelson HS, Patel AV, Diver WR, Stevens VL, Thun MJ, Calle EE. Transforming growth factor beta receptor type I and transforming growth factor beta1 polymorphisms are not associated with postmenopausal breast cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 1262-1267

You W, Liu Z, Zhao J, Zheng M, Zheng SY, Liu X, Zhang HT. No association between TGFBR1*6A and lung cancer. *J Thorac Oncol* 2007; 2: 657-659

Cox DG, Penney K, Guo Q, Hankinson SE, Hunter DJ. TGFBI and TGFBR1 polymorphisms and breast cancer risk in the Nurses’ Health Study. *BMJ Cancer* 2007; 7: 175

Song B, Margolin S, Skoglund J, Zhou X, Rantalajala J, Picelli S, Werelius B, Lindblom A. TGFBR1*6A and Int7G24A variants of transforming growth factor-beta receptor 1 in Swedish familial and sporadic breast cancer. *Br J Cancer* 2007; 97: 1175-1179

Skoglund J, Song B, Dalén J, Dedorson S, Edler D, Hjern F, Holm J, Lenander C, Lindfors U, Lundqvist N, Olvecriona H, Olsson L, Pählman L, Rutesgård J, Smedh K, Törnvist A, Houlston RS, Lindblom A. Lack of an association between the TGFBR1*6A variant and colorectal cancer risk. *Clin Cancer Res* 2007; 13: 3748-3752

Skoglund Lundin J, Vandrovačová J, Song B, Zhou X, Zelada-Hedman M, Werelius B, Houlston RS, Lindblom A. A polymorphism in the transforming growth factor-beta receptor type 1 is associated with an increased familial colorectal cancer risk. *Br J Cancer* 2009; 100: 1674-1679

Castillejo A, Mata-Balaguer T, Montenegro P, Ochoa E, Lázaro R, Martínez-Cantó A, Castillejo MI, Guarinos C, Barbéria VM, Guillén-Ponce C, Carrato A, Soto JL. The TGFBR1*6A variant of transforming growth factor-beta receptor type I is a risk factor for colorectal cancer in the male Spanish population: a case-control study. *BMJ Cancer* 2009; 11: 406

Carvajal-Carmona LG, Churchman M, Bonilla C, Walther A, Lefèvre JH, Kerr DJ, Dunlop M, Houlston R, Bodmer WF, Tomlinson I. Comprehensive assessment of variation at the transforming growth factor beta type I pathway in relation to colorectal cancer progression. *Genes Chromosomes Cancer* 2010; 49: 270-281

Castillejo A, Mata-Balaguer T, Guarinos C, Castillejo MI, Martinez-Cantó A, Barberá VM, Montenegro P, Ochoa E, Lázaro R, Guillon-Ponce C, Carrato A, Soto JL. The Int7G24A variant of transforming growth factor-beta receptor type I is associated with colorectal cancer predisposition. *Pro Natl Acad Sci USA* 2010; 107: 7748-7752

Abuli A, Fernández-Rozadilla C, Giráldez MD, Muñoz J, Gonzalo V, Bessa X, Bujanda L, Rebé J, Lanas A, García AM, Salo J, Argüello I, Villela A, Carreño R, Jover R, Nicola RM, Llor X, Carvajal-Carmona L, Tomlinson IP, Kerr DJ, Houlston RS, Piqué JM, Carraçedo A, Castells A, Andreu M, Ruiz-Ponte C, Castellví-Sil. A two-phase case-control study for colorectal cancer genetic susceptibility: candidate genes from chromosomal regions 9q22 and 3q22. *Br J Cancer* 2011; 105: 870-875

Yan H, Dobbie Z, Gruber SB, Markowitz S, Romans K, Giardello FM, Kinzler KW, Vogelstein B. Small changes in expression affect predisposition to tumorigenesis. *Nat Genet* 2002; 30: 25-26

Yan H, Yuan W, Velculescu VE, Vogelstein B, Kinzler KW. Allelic variation in human gene expression. *Science* 2002; 297: 1143

Raval A, Tanner SM, Byrd JC, Angerman EB, Perko JD, Chen SS, Hackanson B, Grever MR, Lucas DM, Matkovic JJ, Lin TS, Kipps TJ, Murray F, Weisenberger D, Sanger W, Lynch J, Watson P, Jansen M, Yoshinaga Y, Rosenquist R, de Jong PJ, Coggill P, Beck S, Lynch H, de la Chapelle A, Plass C. Down-regulation of death-associated protein kinase 1 (DAPK1) in chronic lymphocytic leukemia. *Cell* 2007; 129: 879-890
Valle L. TGFBR1 and colorectal cancer risk

71 Chen X, Weaver J, Bove BA, Vanderveer LA, Weil SC, Miron A, Daly MB, Godwin AK. Allelic imbalance in BRCA1 and BRCA2 gene expression is associated with an increased breast cancer risk. *Hum Mol Genet* 2008; 17: 1336-1348

72 Zeng Q, Phukan S, Xu Y, Sadim M, Rosman DS, Pennison M, Liao J, Yang GY, Huang CC, Valle L, Di Cristiano A, de la Chapelle A, Pasche B. Tgfbr1 haploinsufficiency is a potent modifier of colorectal cancer development. *Cancer Res* 2009; 69: 678-686

73 Valle L, Serena-Acedo T, Liyanarachchi S, Hampel H, Comeras I, Li Z, Zeng Q, Zhang HT, Pennison MJ, Sadim M, Pasche B, Tanner SM, de la Chapelle A. Germline allele-specific expression of TGFBR1 confers an increased risk of colorectal cancer. *Science* 2008; 321: 1361-1365

74 Guda K, Natalie L, Lutterbaugh J, Wiesner GL, Lewis S, Tanner SM, Tomsic J, Valle L, de la Chapelle A, Elston RC, Willis J, Markowitz SD. Infrequent detection of germline allele-specific expression of TGFBR1 in lymphoblasts and tissues of colon cancer patients. *Cancer Res* 2009; 69: 4959-4961

75 Pasche B, Wisinski KB, Sadim M, Kaklamani V, Pennison MJ, Zeng Q, Bellam N, Zimmerman J, Yi N, Zhang K, Baran J, Stram DO, Hayes MG. Constitutively decreased TGFBR1 allelic expression is a common finding in colorectal cancer and is associated with three TGFBR1 SNPs. *J Exp Clin Cancer Res* 2010; 29: 57

76 Tomsic J, Guda K, Liyanarachchi S, Hampel H, Natalie L, Markowitz SD, Tanner SM, de la Chapelle A. Allele-specific expression of TGFBR1 in colon cancer patients. *Carcinogenesis* 2010; 31: 1800-1804

77 Seguí N, Stevens KN, Guinó E, Rozek LS, Moreno VR, Capellà G, Gruber SB, Valle L. No association between germ-line allele-specific expression of TGFBR1 and colorectal cancer risk in Caucasian and Ashkenazi populations. *Br J Cancer* 2011; 104: 735-740

78 Abadie C, Killian A, Tinat J, Bougeard M, Medhaoui D, Cailleux AF, Baert-Desurmont S, Frebourg T. Allelic imbalance of the TGFπRI is not a major contributor to the genetic predisposition to colorectal cancer. *Br J Cancer* 2011; 104: 1517-1518; author reply 1519-1520

79 Wiesner GL, Daley D, Lewis S, Ticknor C, Platter P, Lutterbaugh J, MacMillen M, Baliner B, Willis J, Elston RC, Markowitz SD. A subset of familial colorectal neoplasia kindreds linked to chromosome 9q22.2-31.2. *Proc Natl Acad Sci USA* 2003; 100: 12961-12965

80 Daley D, Lewis S, Platter P, MacMillen M, Willis J, Elston RC, Markowitz SD, Wiesner GL. Identification of susceptibility genes for cancer in a genome-wide scan: results from the colon neoplasia sibling study. *Am J Hum Genet* 2008; 82: 723-736

81 Skoglund J, Djureinovic T, Zhou XL, Vandrovcova J, Renkonen E, Iselius L, Bisgaard ML, Peltonäki P, Lindblom A. Linkage analysis in a large Swedish family supports the presence of a susceptibility locus for adenoma and colorectal cancer on chromosome 9q22-32.1-31.1. *J Med Genet* 2006; 43: e7

82 Kemp ZE, Carvajal-Carmona LG, Barclay E, Gorman M, Martin L, Wood W, Rowan A, Donohue C, Spain S, Jaeger E, Evans DG, Maher ER, Bishop T, Thomas H, Houlston R, Tomlinson I. Evidence of linkage to chromosome 9q22.33 in colorectal cancer kindreds from the United Kingdom. *Cancer Res* 2006; 66: 5003-5006

83 Gray-McGuire C, Guda K, Adrianto I, Lin CP, Natalie L, Poter JD, Newcomb P, Poole EM, Ulrich CM, Lindor N, Goode EL, Fridley BL, Jenkins R, Le Marchand L, Casey G, Haile R, Hopper J, Jenkins M, Young J, Buchanan D, Gallinger S, Adams M, Lewis S, Willis J, Elston R, Markowitz SD, Wiesner GL. Confirmation of linkage to and localization of familial colon cancer risk haplotype on chromosome 9q22. *Cancer Res* 2010; 70: 5409-5418

84 Papaemmanuil E, Carvajal-Carmona L, Sellick GS, Kemp Z, Webb E, Spain S, Sullivan K, Barclay E, Lubbe S, Jaeger E, Vijayakrishnan J, Broderick P, Gorman M, Martin L, Lucasen A, Bishop DT, Evans DG, Maher ER, Steinke V, Rahner N, Schackert HK, Goecke TO, Holinski-Feder E, Propping P, Van Wezel T, Wijnen J, Cazier JB, Thomas H, Houlston RS, Tomlinson I. Deciphering the genetics of hereditary non-syndromic colorectal cancer. *Eur J Hum Genet* 2008; 16: 1477-1486

85 Bian Y, Caldes T, Wijnen J, Franken P, Vasen H, Kaklamani V, Nafa K, Peterlongo P, Ellis N, Baron JA, Burn J, Moselein G, Morrison PJ, Chen Y, Ahsan H, Watson P, Lynch HT, de la Chapelle A, Fodde R, Pasche B. TGFBR1*6A may contribute to hereditary colorectal cancer. *J Clin Oncol* 2005; 23: 3074-3078

86 Daley D, Morgan W, Lewis S, Willis J, Elston RC, Markowitz SD, Wiesner GL. Is TGFBR1*6A a susceptibility allele for nonsyndromic familial colorectal neoplasia? *Cancer Epidemiol Biomarkers Prev* 2007; 16: 892-894

S- Editor Wang JL. L- Editor Roemmele A. E- Editor Zheng XM