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EDITORIAL

# Debate about *TGFBR1* and the susceptibility to colorectal cancer

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## 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 the 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.



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

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## 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 CRC[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 them. 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 coding 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[15].

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[14,16,17].

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[23-27] 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 *BMPR1A* cause juvenile polyposis, a CRC susceptibility syndrome[30,31], and GWAS have identified low penetrance susceptibility alleles in the BMP pathway and *SMAD*[9,12]. *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[33-55]. In order to overcome this problem, meta-analyses considering increasing number of studies have been published in the last years[56-60]. 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 13 662 cancer cases and 14 147 controls, 2833 and 4255 respectively for CRC[59]. 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[45,46,61-63]. 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*[66] 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 *TGBR1**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*[67] 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[68-71].

Studies in mice point to the relevance of haploinsufficiency of *TGFBR1* in colorectal tumorigenesis. While the homozygous loss of *Tgfbr1* in mice (*Tgfbr1*$^{-/-}$) is lethal, the heterozygous loss (*Tgfbr1*$^{+/-}$) causes no obvious phenotypic traits. However, when *Tgfbr1*$^{+/-}$ mice were bred into mice heterozygous for the *Apc*$^{Min}$ mutation, the double mutants acquired approximately a 2-fold increase in the number of intestinal adenomas in comparison with the *Apc*$^{Min/+}$ mice, as well as colonic carcinomas, suggesting that haploinsufficiency for *Tgfbr1* predisposes to CRC[72].

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[73]. Given the potential use of ASE of *TGFBR1* in the clinical evaluation of CRC risk, additional studies were consequently published[66,74-78]. 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[74,76,77,78]. Recently Abadie *et al*[78] 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[78]. 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[77], 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[66,74,76-78].

**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 | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Binary | Continuous |
| Valle *et al*[73] 2008 | Caucasian | Blood | SNaPshot | rs334348<br>rs7871490<br>rs334349<br>rs1590 | 138/105 | [2]21.0%/2.9% | Yes | Yes |
| Guda *et al*[74] 2009 | Caucasian | Lymph. cell line<br>Normal colon | Pyroseq | rs868<br>rs334348<br>rs334349<br>rs420549<br>rs1590 | Familial: 46/17<br>Sporadic: 44/0 | [3]4.3%/0%<br>[3]0%/- | No | |
| Carvajal-Carmona *et al*[66] 2010 | Caucasian | Lymph. cell line | Genescan<br>SNaPshot | *6A/9A<br>rs1590 | Familial: 24/45 | [3]29.2%/26.7% | No | No |
| Pasche *et al*[75] 2010 | Caucasian | Lymph. cell line | SNaPshot | rs334348<br>rs7871490<br>rs334349<br>rs1590 | 74/0 | [3]14.9%/- | Yes | |
| Tomsic *et al*[76] 2010 | Caucasian | Blood | Pyroseq | rs868<br>rs334348<br>rs334349<br>rs420549<br>rs1590 | [1]109/125 | [3]1.8%/1.6%<br>[2]46.8%/31.2% | No | Yes |
| Seguí *et al*[77] 2011 | Caucasian<br>Ashkenazi | Normal colon<br>Lymphocytes | Pyroseq | rs334349<br>rs7850895<br>rs420549<br>rs1590 | 171/90 | [3]0%/2.2%<br>[2]2.3%/2.2% | No | No |
| Abadie *et al*[78] 2011 | Caucasian | Blood | SNaPshot | rs334348<br>rs7871490<br>rs334349<br>rs1590 | 69/98 | [3]0%/0% | No | 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. [1]49 cases were the same as in Valle *et al*[73], 2008; [2]Cut-off values calculations based on own results: Valle *et al*[73] 2008 and Tomsic *et al*[76] 2010, ROC analysis; Seguí *et al*[77] 2011 median controls ± 2 SD; [3]Applied the cutoff values established by Valle *et al*[73] 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[79,80]. This was later validated in studies from Sweden and the United Kingdom[81,82] 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[51], or of familial CRC selected based on more

relaxed criteria to define heritability, such as the CORGI cohort[66]. Similarly, the *TGFBR1**6A allele was excluded as a disease-causing variant in the CRC families that showed linkage at 9q22[51,82,86].

### ASE 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[73]. Guda *et al*[74] 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*[66] 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*[78], 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.

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