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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.

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GENETICS OF COLORECTAL CANCER

The estimated annual worldwide incidence of colorectal cancer (CRC) is 1235108, with a mortality rate of 609051^[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- β 1, 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 *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*^[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 *Tgfb1* in mice (*Tgfb1*^{-/-}) is lethal, the heterozygous loss (*Tgfb1*^{+/-}) causes no obvious phenotypic traits. However, when *Tgfb1*^{+/-} 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 *Tgfb1* 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 <i>et al</i> ^[73] 2008	Caucasian	Blood	SNaPshot	rs334348 rs7871490 rs334349 rs1590	138/105	² 21.0%/2.9%	Yes	Yes
Guda <i>et al</i> ^[74] 2009	Caucasian	Lymph. cell line Normal colon	Pyroseq	rs868 rs334348 rs334349 rs420549 rs1590	Familial: 46/17 Sporadic: 44/0	³ 4.3%/0% ³ 0%/-	No	
Carvajal-Carmona <i>et al</i> ^[66] 2010	Caucasian	Lymph. cell line	Genescan SNaPshot	*6A/9A rs1590	Familial: 24/45	³ 29.2%/26.7%	No	No
Pasche <i>et al</i> ^[75] 2010	Caucasian	Lymph. cell line	SNaPshot	rs334348 rs7871490 rs334349 rs1590	74/0	³ 14.9%/-	Yes	
Tomsic <i>et al</i> ^[76] 2010	Caucasian	Blood	Pyroseq	rs868 rs334348 rs334349 rs420549 rs1590	¹ 109/125	³ 1.8%/1.6% ² 46.8%/31.2%	No	Yes
Seguí <i>et al</i> ^[77] 2011	Caucasian Ashkenazi	Normal colon Lymphocytes	Pyroseq	rs334349 rs7850895 rs420549 rs1590	171/90	³ 0%/2.2% ² 2.3%/2.2%	No	No
Abadie <i>et al</i> ^[78] 2011	Caucasian	Blood	SNaPshot	rs334348 rs7871490 rs334349 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. ¹49 cases were the same as in Valle *et al*^[73] 2008; ²Cut-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 \pm 2 SD; ³Applied 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 linked 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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Association between *IRS-2* G1057D polymorphism and risk of gastric cancer

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polymorphism in cases were obviously different from those in the control group ($P = 0.031$). Compared with GG genotype carriers, the risk for GC was significantly higher (adjusted odds ratio = 2.32, 95% CI: 1.03-5.23, $P = 0.042$) in the individuals with the *IRS-2* DD genotype. Furthermore, stratified analysis was performed based on age, sex, smoking status and residence, but no significant difference between the two groups was found. In addition, no significant association between genotypes and clinicopathological features was observed either.

CONCLUSION: This study demonstrates that *IRS-2* G1057D is involved in susceptibility to GC, although further large-sample studies are still needed.

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Key words: Gastric cancer; *Insulin receptor substrate-2*; Polymorphism; Genotype; Case-Control study

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Abstract

AIM: To investigate the relationship between insulin receptor substrate-2 (*IRS-2*) G1057D polymorphism and the risk of gastric cancer (GC) in a Chinese population.

METHODS: A case-control study with 197 GC patients and 156 age- and sex- matched control subjects was conducted. The genotypes of polymorphism were assessed by polymerase chain reaction-restriction fragment length polymorphism.

RESULTS: The genotype frequencies of *IRS-2* G1057D

INTRODUCTION

Gastric cancer (GC) remains a major medical challenge and one of the prevalent malignant diseases. Extensive invasion and metastasis are the pivotal factors for its poor prognosis. As shown in epidemiological studies, GC is the fourth most common malignancy and the second most frequent cause of cancer-related death worldwide^[1,2]. Moreover, nearly half of GC cases occur

in China alone^[3]. Although the cause is largely unknown, GC is thought to result from a combination of multiple environmental factors and the accumulation of specific genetic alterations, including polymorphisms^[4-8].

Insulin receptor substrates (IRS) are a family of six (IRS-1 to IRS-6) structurally related cytoplasmic adaptor proteins that integrate and coordinate numerous biologically key extracellular signals within the cell^[9-13]. Among the six family members, humans express three members (IRS-1, IRS-2 and IRS-4), while IRS-1 and IRS-2 are widely expressed^[10,11,12]. Despite a high level of sequence homology, IRS-1 and IRS-2 mediate distinct cellular functions. IRS-1 controls body growth and peripheral insulin action and IRS-2 regulates body weight control and glucose homeostasis^[14,15].

Although IRS proteins do not have intrinsic kinase activity, they act as adaptors and organize signaling complexes to initiate intracellular signaling cascades^[14] and function between multiple growth factor receptors possessing tyrosine kinase activity, such as the insulin receptor (IR), Type I insulin-like growth factor receptor (IGF-IR) and a complex network of intracellular signaling molecules containing Src homology 2 domains^[16-18]. It is now clear that IRSs are the core signaling molecules of the actions of the IGF-IR signaling^[19,20]. In recent years, numerous studies have shown that these signaling adaptors are themselves oncogenic and can induce malignant transformation. Dearth *et al.*^[14] reported that IRS-2 was able to transform NIH3T3 cells in a foci-formation assay. Also, many studies have shown that both IRS-1 and IRS-2 were overexpressed in hepatocellular carcinoma^[21-23]. Yamashita *et al.*^[24] found that there was a possibility that the silencing of IRS-2 was causally related to development and progression of GC.

IRS-2 was first discovered as an alternative IRS, initially named 4PS, in insulin-stimulated cells derived from *Irs-1*^{-/-} mice^[25]. IRS-2 is widely expressed and is the primary mediator of insulin dependent mitogenesis and regulation of glucose metabolism in most cell types^[16]. The *IRS-2* gene is located on chromosome 13q34. To date, a number of polymorphisms have been identified in the *IRS-2* gene. Among those, the amino acid substitution Gly1057Asp (GGC-GAC at codon 1057, G1057D rs1805097) was found to be associated with various human diseases. A study conducted by Almind *et al.*^[26] reported decreased serum insulin and C-peptide concentrations during an oral glucose tolerance test in middle-aged glucose tolerant Danish male subjects carrying the D1057 allele. There were reports about the association of G1057D with type 2 diabetes in Danish^[27], Finnish, Chinese, Swedish^[26,28] and German^[29] populations, but the results were inconsistent. Recent observations also indicated that G1057D polymorphism was associated with endometrial cancer^[30], colon cancer^[31] and polycystic ovary syndrome^[32].

The mechanism by which the nonconservative G1057D variant affects risk of cancer or other diseases is not clear, but a charged amino acid (D) in place of a neutral one (G) in the domain of IRS-2 molecule located in between

two putative tyrosine phosphorylation sites (at positions 1042 and 1072) of the protein could produce alterations in downstream signaling through IRS-2^[33]. If this variant causes alterations of downstream signaling of IGF-IR signaling which promote GC progression and invasion, it may influence GC susceptibility. Also, to our knowledge, no study has examined the influence of the polymorphism on the risk of GC. Therefore, we conducted a hospital-based case-control study to investigate the potential link between this polymorphism and GC in a Chinese population.

MATERIALS AND METHODS

Study population

One hundred and ninety seven consecutive, unrelated GC patients were recruited at the Nanjing Medical University Affiliated Hospital. The diagnosis of GC was confirmed histologically. Patients with secondary or recurrent tumors were excluded. 156 genetically unrelated cancer-free individuals were selected from the inpatients admitted to the hospital during the same period with no history or diagnosis of any cancer and genetic disease. They were matched with the cases on age (within 5 years) and sex. All subjects were Han nationality and from Jiangsu Province or its surrounding regions. A structured questionnaire was administered by interviewers to collect information on demographic information and personal medical history. Individuals who formerly or currently smoked ≥ 10 cigarettes per day on average for at least 2 years were defined as smokers. Pathological variables were obtained from the medical records of the GC patients. All gastric carcinomas were classified according to the TNM classification criteria of International Union Against Cancer^[34]. Differentiation-grade was classified according to World Health Organization classification. The study was approved by the Nanjing Medical University Affiliated Hospital Ethics Committee and informed consent was obtained from each participant.

Genotyping analysis

Genomic DNA was isolated from peripheral blood lymphocytes according to the protocol described in our previous study^[35]. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was used to identify the *IRS-2* G1057D genotypes. PCR was done in 20 μ L reaction mixtures containing 10 μ L 2 \times PCR Master mix (Genetech biotechnology, Nanjing, China), 0.25 μ mol/L each primer (forward 5'-GTCCCC-GTCGTCGTCCTCT-3', reverse 5'-CTCGACTCCC GACACCTG-3') and 200 ng genomic DNA. The amplification protocol is as follows: initial denaturation at 95°C for 4 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 57°C for 30 s, extension at 72°C for 30 s and then with a final elongation at 72°C for 5 min. The 286 bp PCR products were digested by the restriction enzyme *Hae II* (New England BioLabs), 10 units for 1 h at 37°C, followed by electrophoresis on a 3% agarose gel containing ethidium bromide, and bands were then visual-

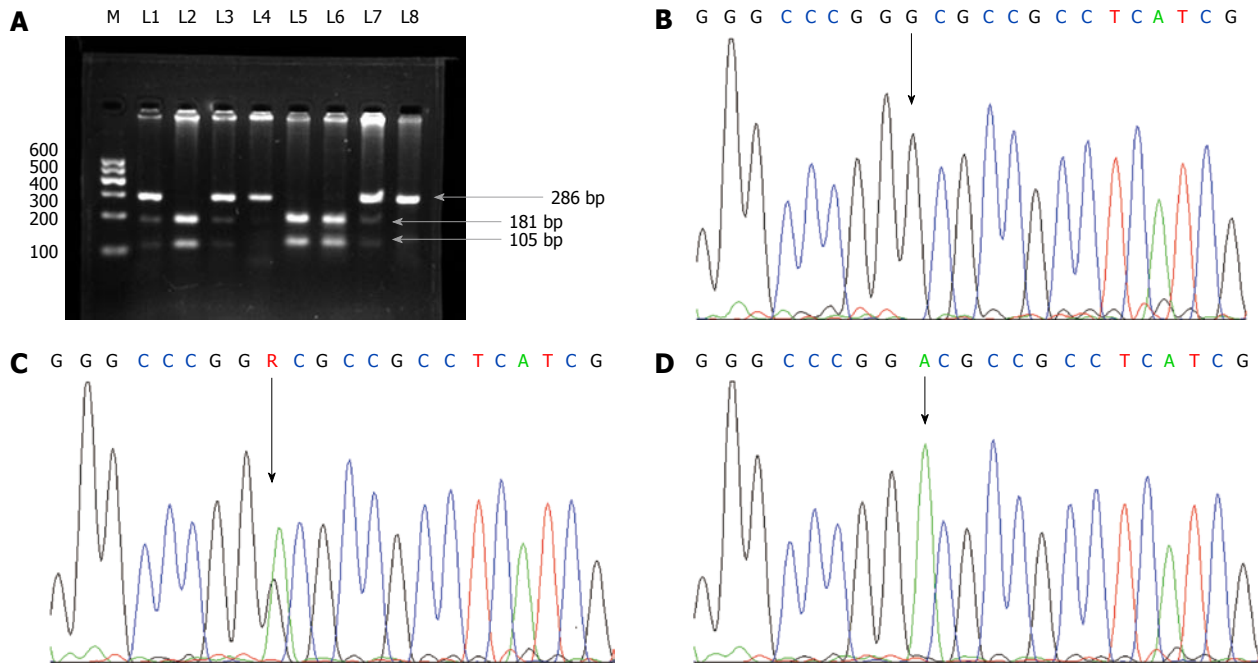


Figure 1 Genotypes of *insulin receptor substrate-2* G1057D confirmed by polymerase chain reaction-restriction fragment length polymorphism assay and direct sequencing. A: Representatives of genotypes by polymerase chain reaction-restriction fragment length polymorphism assay. L4, L8 were identified as DD; L1, L3 and L7 were identified as GD; L2, L5 and L6 were identified as GG; B, C and D: Representatives of GG, GD, DD genotypes by direct DNA sequencing respectively.

ized by ultraviolet transillumination. The genotypes were assessed as follows: The wild-type homozygotes (GG) produced two bands at 105 and 181 bp, while the variant homozygotes (DD) produced one band at 286 bp and the heterozygous (GD) produced three bands at 286, 181 and 105 bp (Figure 1). About 10% of the samples were randomly selected to do the repeated assays and the results were 100% concordant. Genotyping was performed without knowledge of the subject's case and control status. In addition, PCR products of the polymorphism with different genotypes were selected and verified by direct sequencing using ABI 3730 DNA analyzer (Applied Biosystems, Foster City, CA, USA) (Figure 1).

Statistical analysis

All statistical analyses were performed using SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). All of the tests were two-tailed and statistical significance was defined as $P < 0.05$. Quantitative variables departing from the normal distribution, including age and weight, were summarized as median and analyzed by Mann-Whitney rank sum test. Pearson's χ^2 test was used to compare the difference in the distribution of categorical variables and genotype frequencies between cases and controls. The Hardy-Weinberg equilibrium of the *IRS-2* genotypes was analyzed by the goodness-of-fit χ^2 test. Odds ratio (OR) and 95% CI were calculated to evaluate the association between the polymorphism and the risk of GC. Carriers of the wild genotype GG were used as the reference. The crude OR was assessed by the Woolf approximation method and the adjusted OR was computed using the unconditional logistic regression method, with adjustment for age, sex, smoking status, residence, hyperten-

Table 1 Demographic information n (%)

Characteristics	Cases ($n = 197$)	Controls ($n = 156$)	P value
Gender (male)	152 (77.16)	118 (75.64)	0.739
Age ¹ (yr)	60 (50-67.5)	58 (47.25-65)	0.197
Weight ¹ (kg)	62 (55-70)	67 (60-73.25)	0.001
Hypertension	43 (21.83)	29 (18.83)	0.490
Diabetes	10 (5.08)	14 (9.03)	0.144
Smoking	44 (22.34)	26 (16.67)	0.205
Residence			
Rural	84 (42.64)	70 (45.45)	0.598
Urban	113 (57.36)	84 (54.55)	

¹Median (25th-75th percentiles).

sion and diabetes.

RESULTS

Demographic information

The demographic characteristics of the participants are listed in Table 1. As expected, there was no significant difference in age and sex distribution between the case and control groups. Moreover, the two groups were similar with respect to smoking status, residence, history of hypertension and diabetes. Nevertheless, compared with controls, GC patients had a lower body weight ($P = 0.001$).

Distributions of the *IRS-2* genotype in cases and controls and risk estimates

Data for genotype frequencies and the associations between *IRS-2* G1057D polymorphism and the risk of GC are shown in Table 2. The genotype distributions

Table 2 Distribution of the *IRS-2* genotype in cases and controls and risk estimates *n* (%)

<i>IRS-2</i> genotype	Cases ¹	Controls ¹	Crude OR (95% CI)	<i>P</i> value	Adjusted OR ² (95% CI)	<i>P</i> value
Overall	197	156				
GG	69 (35.02)	64 (41.03)	1.00		1.00	
GD	98 (49.75)	82 (52.56)	1.11 (0.71-1.74)	0.653	0.96 (0.60-1.53)	0.864
DD	30 (15.23)	10 (6.41)	2.78 (1.26-6.15)	0.011	2.32 (1.03-5.23)	0.042
GD + DD	128 (64.98)	92 (58.97)	1.29 (0.84-1.99)	0.248	1.11 (0.71-1.75)	0.637
G allele	236 (59.90)	210 (67.31)	1.00			
D allele	158 (40.10)	102 (32.69)	1.38 (1.01-1.88)	0.043		

¹Distribution of the insulin receptor substrate-2 (*IRS-2*) genotype in cases and controls were in Hardy-Weinberg equilibrium ($P = 0.204$, $P = 0.425$, respectively); ²Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

Table 3 Stratified analyses for variant *IRS-2* genotypes in cases and controls *n* (%)

Variable	(GD + DD)/GG		Crude OR (95% CI)	<i>P</i> value	Adjusted OR ¹ (95% CI)	<i>P</i> value
	Cases	Controls				
Age (median) (yr)						
≤ 58	53 (26.9)/40 (20.3)	46 (29.5)/39 (25.0)	1.29 (0.71-2.33)	0.412	1.10 (0.59-2.05)	0.762
> 58	69 (35.0)/35 (17.8)	46 (29.5)/25 (16.0)	1.22 (0.64-2.32)	0.538	1.15 (0.60-2.23)	0.674
Sex						
Females	28 (14.2)/17 (8.6)	21 (13.5)/17 (10.9)	1.33 (0.55-3.21)	0.521	1.13 (0.44-2.87)	0.800
Males	94 (47.7)/58 (29.4)	71 (45.5)/47 (30.1)	1.27 (0.77-2.10)	0.342	1.12 (0.67-1.87)	0.668
Smoking status						
Smokers	32 (16.2)/12 (6.1)	16 (10.4)/10 (6.5)	1.88 (0.66-5.33)	0.238	1.52 (0.49-4.70)	0.467
Non-smokers	90 (45.7)/63 (32.0)	75 (48.7)/53 (34.4)	1.16 (0.72-1.87)	0.550	1.00 (0.61-1.65)	0.990
Residence						
Urban	73 (37.1)/40 (20.3)	51 (33.1)/33 (21.4)	1.44 (0.80-2.61)	0.226	1.30 (0.70-2.42)	0.406
Rural	49 (24.9)/35 (17.8)	41 (26.6)/29 (18.8)	1.04 (0.55-1.98)	0.905	0.89 (0.46-1.75)	0.743

¹Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

complied well with Hardy-Weinberg equilibrium in cases and controls ($P = 0.204$, $P = 0.425$, respectively). The distribution of the *IRS-2* genotype was significantly different between GC cases and controls ($P = 0.031$). Moreover, the frequency of D allele was significantly higher in GC patients than in control subjects (40.10% *vs* 32.69%, $P = 0.043$). With the wild genotype GG as reference, we found that the DD genotype was associated with an increased risk of GC (adjusted OR = 2.32; 95% CI: 1.03-5.23, $P = 0.042$). The *IRS-2* D allele elevated GC risk compared with G allele, the relative risk for the *IRS-2* D allele was 1.38 (adjusted OR = 1.38; 95% CI: 1.01-1.88, $P = 0.043$) for the GC patients compared with population controls.

Stratified analyses of the polymorphism and GC risk

To further clarify the relationship between *IRS-2* variant and the GC risk, we performed stratified analysis. Table 3 presents the results of stratified analyses by the median age of controls (58 years), sex, smoking status and residence with the *IRS-2* variant genotypes. No statistically significant difference was observed in younger subjects (age ≤ 58) and older subjects (age > 58) in the association between the polymorphism and susceptibility to GC (adjusted OR = 1.10, 95% CI: 0.59-2.05 and adjusted OR = 1.15, 95% CI: 0.60-2.23, respectively). Analogously, we did not note statistically significant associations in the strati-

fied analyses of sex, smoking status and residence.

Variant genotypes and clinicopathological characteristics of GC

Finally, we also estimated the correlations of the *IRS-2* variant genotypes with clinicopathological features of GC, including tumor differentiation, depth of tumor infiltration, lymph node status and tumor location. As shown in Table 4, no statistically significant association was found.

DISCUSSION

The genetics and heredity of complex human traits have been studied for over a century. Over the last decade, genetic studies have identified numerous associations between single nucleotide polymorphism alleles in the human genome and important human diseases. Studies about genetic polymorphism have proven to be powerful and efficient in identifying genetic variants associated with various diseases. In the present study, for the first time we investigated the role of *IRS-2* gene G1057D polymorphism in GC susceptibility in a Chinese population and we found that the DD genotype conferred an increased risk of GC.

Involving the two important cancer-related pathways (MAPK/ERK, PI3K/Akt), IGF-IR was documented

Table 4 Associations between variant *IRS-2* genotypes and clinicopathological characteristics of gastric cancer

Variable	GD + DD	GG	Crude OR (95% CI)	P value	Adjusted OR ¹ (95% CI)	P value
Tumor differentiation						
Well	15	6	1		1	
Moderate	80	35	0.91 (0.33-2.55)	0.864	0.95 (0.33-2.76)	0.921
Poor	29	25	0.46 (0.16-1.38)	0.166	0.38 (0.11-1.35)	0.135
Depth of tumor infiltration						
T1	21	14	1		1	
T2	20	5	2.67 (0.81-8.77)	0.106	2.70 (0.70-10.47)	0.150
T3	60	26	1.54 (0.68-3.49)	0.302	1.46 (0.60-3.52)	0.401
T4	24	22	0.73 (0.30-1.77)	0.483	0.73 (0.29-1.86)	0.507
Lymph node metastasis						
Negative	47	23	1		1	
Positive	78	43	0.89 (0.48-1.65)	0.708	0.94 (0.49-1.77)	0.837
Localization						
Cardia	27	15	1		1	
Non-cardia	101	54	1.04 (0.51-2.12)	0.916	1.08 (0.51-2.29)	0.838

¹Adjusted for age, sex, smoking status, residence, hypertension and diabetes. OR: Odds ratio.

to promote tumor growth, progression and invasion. Increased expression levels of both IGF and IGF-IR are found in gastrointestinal carcinomas^[36,37]. Exogenous IGFs promote the proliferation of GC cells and the blocking of IGF-IR inhibits tumor development^[36,38-40]. As the major downstream effector of the IGFs, *IRS-2* plays a critical role in determining the cellular response to IGF stimulation and is proven to be one of the key factors accelerating tumor progression and metastasis in various types of cancers. For example, *IRS-2* dependent signaling promotes cell motility and invasion in neuroblastoma and mesothelioma cells^[41-43]. The up-regulation of *IRS-2* expression in pancreatic and hepatocellular carcinoma suggests a positive contribution of this *IRS* family member to tumor progression^[23,44]. Another study conducted by Yamashita *et al.*^[24] found that there was a possibility that the silencing of *IRS-2* was causally related to the development and progression of GCs.

An amino acid substitution of Gly to Asp change at codon 1057 has been associated with insulin sensitivity and may subtly mediate interaction with downstream signaling molecules^[45]. The variant lies between two putative sites of tyrosine phosphorylation (at position 1042 and 1072) and a non-conservative amino acid substitution in this domain may result in a subtle alteration of the affinity between *IRS-2* and downstream signaling elements, which may change the interaction with downstream signaling molecule^[33]. However, there is the possibility that this polymorphism is not functional but may be in linkage disequilibrium with a currently unrecognized functional polymorphism. Based on these previous observations, it would therefore be plausible to expect that the *IRS-2* G1057D polymorphism may be associated with GC.

Several epidemiological studies have investigated the association between the G1057D polymorphism and various diseases. There were reports about the association of the G1057D with type 2 diabetes in Danish^[27], German^[29], Finnish, Chinese and Swedish^[26,28] populations, but the results were inconsistent. In a large case-

control study in Asian Indians, Bodhini *et al.*^[46] found that DD genotype increased susceptibility to type 2 diabetes by interacting with obesity ($P = 0.002$). Another study conducted by Slattery *et al.*^[31] found that *IRS-2* G1057D heterozygote GD genotype significantly reduced the risk of colon cancer (OR = 0.8, 95% CI: 0.6-0.9). Recently, Cayan *et al.*^[30] reported the risk for endometrial cancer was 4.87 times higher in the individuals with the *IRS-2* DD genotype compared to the GG genotype (OR = 4.87, 95% CI: 1.74-13.63).

To further investigate the association between *IRS-2* G1057D polymorphism and the risk of GC, we conducted this hospital-based case-control study in a Chinese population. The frequency of the variant D allele was higher in GC patients than in control subjects. We also found that the DD genotypes conferred a 132% increased risk of developing GC in this Chinese population. The allele frequencies in controls was in the range of those in previous reports^[31,46]. It is probable that the discrepancies in sample size, ethnic background, selection of cases and controls, and study design may partly explain the differences observed in this study and others.

We then performed stratification analyses by age, sex, smoking status and residence, but no statistically significant difference was observed. Although several studies have suggested that *IRS-2* indicate a major role in cell motility and invasion^[41-43], the current study found no significant correlation between the *IRS-2* G1057D polymorphism and tumor differentiation, depth of tumor infiltration, lymph node status and tumor location. However, since only a few studies have addressed the impact of the *IRS-2* gene G1057D polymorphism on the clinical features of solid tumors, and the sample size of our study might not be large enough for subgroup analyses, further studies are warranted to clarify the association between the *IRS-2* G1057D polymorphism and the clinicopathological features or the prognosis of GC.

Several limitations in our study need to be addressed. First of all, although this was a population based case-

control study, selection bias could not be avoided. Nevertheless, the *IRS-2* G1057D polymorphism variant allele frequency in control subjects was in the range of those in previous reports^[31,46] and the genotype distribution of controls was in Hardy-Weinberg equilibrium. Secondly, the sample size of our study might not be large enough, especially for subgroup analyses. However, our preliminary data provides valuable guidance to future larger sample size studies in this area. Thirdly, *Helicobacter pylori* (*H. pylori*) infection is now established as a critical event in the development of GC but in our study, not enough information on *H. pylori* status was provided because it was unethical to do *H. pylori* tests in every subject.

In conclusion, our data suggests that the *IRS-2* G1057D polymorphism is associated with an increased risk of GC in the Chinese population. Further studies with a larger sample size are warranted to confirm these initial observations and extend the results.

COMMENTS

Background

Insulin receptor substrate-2 (*IRS-2*), an important member of *IRS* proteins, has been demonstrated play a crucial role in tumor growth, progression and invasion. *IRS-2* G1057D polymorphism has been implicated in a range of human diseases and recent studies have indicated that the polymorphism is associated with cancer risk.

Research frontiers

Using a polymerase chain reaction-restriction fragment length polymorphism method, this study explored the relationship between *IRS-2* G1057D polymorphism and gastric cancer (GC) risk.

Innovations and breakthroughs

IRS-2 G1057D polymorphism is associated with the elevated risk of GC in the Chinese population.

Applications

It is seen from this study that *IRS-2* G1057D polymorphism contributes to susceptibility to GC, which is meaningful for early diagnosis, prevention and individual-based treatment of GC.

Terminology

IRS-2 is an important member of *IRS* proteins that function as adaptors and organize signaling complexes to initiate intracellular signaling cascades. Single nucleotide polymorphisms are the most common type of sequence differences between alleles, which can be used as simple genetic markers.

Peer review

This is an interesting paper on the association between the *IRS-2* G1057D polymorphism and GC risk in a small cohort of patients with GC and controls. A borderline statistically significant relationship was reported.

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Events Calendar 2012

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10th Oncology Controversies and
Advances Update
Steamboat Springs,
CO, United States

January 19-21, 2012
EASL Monothematic Conference:
IMLI - Immune Mediated Liver
Injury
Birmingham, United Kingdom

January 19-21, 2012
American Society of Clinical
Oncology 2012 Gastrointestinal
Cancers Symposium
San Francisco, CA, United States

January 19-21, 2012
2012 Gastrointestinal Cancers
Symposium
San Francisco, CA, United States

January 20-21, 2012
American Gastroenterological
Association Clinical Congress of
Gastroenterology and Hepatology
Miami Beach, FL, United States

February 2-4, 2012
2012 Genitourinary Cancers
Symposium
San Francisco, CA, United States

February 6-8, 2012
Pediatric Cancer Translational
Genomics
Phoenix, AZ, United States

February 8-10, 2012
The 84th Annual Meeting of Japanese
Gastric Cancer Association
Osaka, Japan

February 10-11, 2012
Cancer Survivorship for Clinicians
Seattle, WA, United States

February 14-17, 2012
ASCO Multidisciplinary Cancer
Management Course
Eldoret, Kenya

February 20-24, 2012
Word Conference on Colorectal
Cancer
FL, United States

February 22-23, 2012
National Cancer Institute Annual
Biospecimen Research Network
Symposium: "Advancing Cancer
Research Through Biospecimen
Science"
Bethesda, MD, United States

February 22-25, 2012
30th German Cancer Congress
Berlin, Germany

February 24, 2012
ASCO-German Cancer Society
Joint Symposium, German Cancer
Congress
Berlin, Germany

February 24-27, 2012
Canadian Digestive Diseases Week
2012
Montreal, Canada

March 7-8, 2012
First International Gulf Joint
Conference: Management of colon,
breast, and lung cancer (Joint
Symposium)
Dammam, Saudi Arabia

March 9-10, 2012
ESMO Conference on Sarcoma and
GIST
Milan, Italy

March 10-11, 2012
Colorectal Polyps and Cancers: A
Multidisciplinary Approach
Scottsdale, AZ, United States

March 17-21, 2012
Methods in Cancer Research
Workshop (Advanced Cancer
Course)
Al Asha, Saudi Arabia

March 22-24, 2012
The 1st St.Gallen EORTC
Gastrointestinal Cancer Conference
St.Gallen, Switzerland

April 13-15, 2012
Asian Oncology Summit 2012
Singapore, Singapore

April 15-17, 2012
European Multidisciplinary
Colorectal Cancer Congress 2012
Prague, Czech

April 18-20, 2012
The International Liver Congress
2012
Barcelona, Spain

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA, United States

April 20-21, 2012
OOTR 8th Annual Conference -
Organisation for Oncology and
Translational Research
Kyoto, Japan

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 19-22, 2012
Digestive Disease Week 2012
San Diego, CA, United States

June 18-21, 2012
Pancreatic Cancer: Progress and
Challenges
Lake Tahoe, NV, United States

June 27-30, 2012
ESMO 14th World Congress on

Gastrointestinal Cancer 2012
International Convention Center Of
Barcelona,
Barcelona, Italy

July 1-5, 2012
10th World Congress of the
International Hepato-Pancreato-
Biliary Association
Paris, France

July 5-7, 2012
International Research Conference
on Liver Cancer
Heidelberg, Germany

July 6-8, 2012
The 3rd Asia - Pacific Primary Liver
Cancer Expert Meeting "A Bridge to
a Consensus on HCC Management
Shanghai, China

September 1-4, 2012
OESO 11th World Conference
Como, Italy

September 14-16, 2012
ILCA 2012 - Sixth Annual Conference
of the International Liver Cancer
Association
Berlin, Germany

September 21-22, 2012
Research Symposium, Inflammation
and Cancer
Houston, TX, United States

October 15 - 17 2012
13th World Congress of the
International Society for Diseases of
the Esophagus
Venice, Italy

December 5-8, 2012
22nd World Congress of the
International Association of
Surgeons, Gastroenterologists and
Oncologists
Bangkok, Thailand



INSTRUCTIONS TO AUTHORS

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glu-

cose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; **(401)**: 230-238 [PMID: 12151900 DOI:10.1097/0000-3086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express t test as t (in italics), F test as F (in italics), chi square test as χ^2 (in Greek), related coefficient as r (in italics), degree of freedom as v (in Greek), sample number as n (in italics), and probability as P (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: t time or temperature, c concentration, A area, l length, m mass, V volume.

Genotypes: *gyrA*, *arg 1*, *c myc*, *c fos*, *etc.*

Restriction enzymes: *EcoRI*, *HindII*, *BamHI*, *Kbo I*, *Kpn I*, *etc.*

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