Review Article

Colorectal Cancer: A Review of the Genome-wide Association Studies in the Kingdom of Saudi Arabia

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ABSTRACT

Genome-wise association studies (GWAS) identify risk variants and modifiers that can influence the pathophysiological processes involved in colorectal cancer (CRC) and thus are important to detect associations between disease phenotypes. Our literature review, performed as per PRISMA statement indicates a significant lack of GWAS functional studies in Saudi Arabia. Therefore, studies on sequencing and mapping are needed to identify gene variants that play a role in the pathophysiology of CRC in this specific population. Because it is not apt to generalize disease associations found in other racial and/or ethnic groups to the Arabic or Middle Eastern population, it is very important to conduct GWAS taking into account multiple ethnicities in this region. In addition, linkage studies and case–control studies that include the various confounding and epigenetic factors are needed for appropriate diagnosis of CRC. We recommend that studies in this region be conducted to understand the role of gene–environment interactions across the various ethnic groups, stages of cancer, tumor type, clinical variables, and the population risk to CRC.

Key Words: Colorectal cancer, GWAS, Saudi Arabia

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Colorectal cancer (CRC) is the third and fourth most common cancer in women and men worldwide, respectively, and the fourth most common cause of cancer death.[1] CRC exhibits global geographic variations in its incidence with multiple factors (social, demographic, environmental, and genetic) playing different roles in its pathogenesis. Diet rich in fat and low in fiber, high levels of triglycerides, physical inactivity, diabetes, alcohol, obesity, and smoking are the identified risk factors of colorectal cancer. Hereditary factors play a definite role, but gene–environment interactions are also important in the pathogenesis.[2] Approximately 70% of the risk of colorectal cancer can be related to environmental factors, and identification of these may help prevent the development of the disease. CRC is generally sporadic but approximately 25% of the patients have a genetic predisposition. Instability in chromosomes, CpG island methylation, and microsatellite instability have been reported in key genes leading to the developing of CRC.[3] The disease-specific mortality in development countries for CRC has been reported to be approximately 33%.[4]

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Histopathologically, CRC is manifested in the host as crypt lesions, adenomatous polyps, and carcinomas, which are malignant. CRC develops through a series of clinical processes including inactivation of adenomatous polyposis coli (APC) and mutations in tumor suppressor genes and oncogenes, which are involved in carcinogenesis and due to alterations.[5] Alterations in the levels of gene expressions along with epigenetic modifications in the promoter regions of these genes. Some of the genes and associated syndromes, which have a potential risk in CRC are presented in Table 1. Polymorphisms causing genetic susceptibility and associated CRC risk were found in GSTT1, GSTM1, COX 2, MTHFR, NATs, MTR, and TGF-beta1 genes.[3] The gene polymorphisms in these genes and gene–environment interactions in these genes were found to be associated with increased risk of CRC.

The current article is presented as per the PRISMA statement (www.prisma-statement.org). Published genome-wide association studies (GWAS) in CRC from Saudi Arabia were

Table 1: Genes and chromosomes that cause syndromes associated with risk of colorectal cancer

Gene (s)	Syndrome	Clinical features
Chromosomes 8, 9, 11, and 18	FCC	FCC accounts for approximately 20% of CRCs in developed countries. The term familial colorectal cancer is used to categorize CRC families that do not meet the clinical criteria for a diagnosis of known hereditary CRC syndromes
APC	FAP, Attenuated FAP	FAP is an autosomal dominant condition characterized by the multiple adenomas that inevitably result in CRC. AFAP is characterized by fewer colorectal adenomatous polyps
MUTYH	MAP	Autosomal recessive, MAP is characterised by adenomatous polyps of the colorectum and a very high risk of CRC
MMR genes	LS	LS is autosomal dominant caused by mutations in MMR is the common hereditary CRC predisposing syndrome
SMAD4 (DPC4), BMPR1A	JPS, HMPS	Autosomal dominant JPS is characterized by hamartomatous polyps and lifetime CRC risk in JPS individuals is estimated to be 39%
Unknown	HPPS	HPPS is a rare condition characterized by the presence of multiple and/or large hyperplastic polyps throughout the colon that predisposes 50% or more of the patients to CRC development

CRC: Colorectal cancer, FAP: Familial adenomatous polyposis, FCC: Familial colorectal cancer, HPPS: Hyperplastic polyposis syndrome, JPS: Juvenile polyposis syndrome, LS: Lynch syndrome, MAP: MUTYH-associated polyposis, HMPS: Hereditary Mixed Polyposis Syndrome, MMR: Mismatch repair

searched using the search engines PubMed, MEDLINE, EMBASE, and Cochrane Collaboration databases up to May 2014 using the search strategy: ("colorectal cancer" OR "colon cancer") AND ("genetic studies" OR "genome wide association studies," OR "gene polymorphisms") AND ("Saudi Arabia" OR "Kingdom of Saudi Arabia"). The references within the selected articles were manually searched for any relevant literature within this topic. Only studies that included information of GWAS within CRC and conducted in Saudi Arabia were narrowed down to retain the focus of this article. The diagnosis of CRC within the selected studies was as per the internationally accepted criteria. The data were collected independently by two reviewers and any conflicts were resolved through consensus.

Role of pathophysiology and gene polymorphisms in CRC

Tumor progression from normal epithelium to adenoma and carcinoma involves a lot of cellular and molecular events, including genetic alterations, chromosomal instability, hypermethylation of genes, microsatellite instability.[5-7] Chromosomal instability leads to aneuploidy and loss of important segments in chromosomes, which was detectable in chromosomes 5, 18, and 17. These mutations may cause changes that influence tumor growth and progression, including characteristic histological changes.[7] Family history of CRC also increases the risk in close relatives, but the magnitude of risk is dependent on the age of diagnosis and the extent of relationship among individuals. It is thus very important to analyze the genetic loci vis-à-vis environmental factors and family history and focusing on candidate genes of biologic relevance to CRC pathogenesis.[7,8] Some studies have used a genome-wide approach to evaluate pattern of gene polymorphisms throughout the genome, based on the International HapMap Project.[9,10] This project helped to identify alleles that may confer an increased or decreased association with CRC risk and help in stratification of at-risk individuals thus helping to devise appropriate screening and treatment methods. The absolute risk of different syndromes in CRC has been estimated in many studies with values ranging from 90% by 45 years of age for FAP, 69% by 80 years for attenuated FAP, 40%–80% by 75 years for LS, 35%–53% for MYH-associated polyposis, 39% by 70 years for PJS and 17%–86% by 60 years for JPS.[11-16] The identification of biologically relevant alleles in terms of susceptibility with CRC will need further functional and molecular characterization studies, which should be collectively analyzed for firm conclusions to be drawn. From the above it is understood that genetic testing for susceptibility genes is important to assess germline mutations to formulate appropriate intervention strategies, screening programs and risk analyses. Palles *et al.*[17] described the transmission pattern in the families with CRCS10, which showed autosomal dominant inheritance. They identified a heterozygous mutation in the germline POLD1 gene and somatic POLE mutation by linkage analysis and sequencing. In addition, tumors showed microsatellite stability. Collectively, this study showed that replication errors may have increased the rate of mutations in CRC. In addition to germline POLD1 mutations, Palles *et al.*[17] identified somatic POLE mutations in five colorectal cancers from a large database. All of these tumors had additional somatic mutations. These findings suggested that the mechanism of tumorigenesis in POLD1-mutated tumors is decreased fidelity of replication-associated polymerase proofreading, leading to an increased mutation rate.

Genome-wide association studies in CRC

GWAS have been used as important tools to identify and understand disease gene loci and their role in genetic susceptibility, carcinogenesis, and disease mechanisms.[6,18,19] GWAS are used for screening, disease prevention, and risk identification in cancers. It has been widely understood that cancer can show familial gene clustering and in colorectal cancer mutations in mismatch repair genes have been identified. However, genetic linkage studies cannot confirm susceptibility due to the existence of alleles with

lower penetrance [Figure 1]. Genetic association studies previously involved genetic polymorphism analyses, studies on pathways involved in carcinogenesis, DNA repair, hormone biosynthesis, carcinogen metabolism, and cell cycle control.[6] Later, studies involved assessments of functional single nucleotide polymorphisms (SNPs) and gene sequencing.

GWAS processes multiple SNPs simultaneously through genotyping platforms by tagging variants in the genome by scanning for associations. GWAS have been conducted in colorectal cancer, and five genetic predisposition loci have been identified in the western population [Table 2]. Pande *et al*. 2010 in a retrospective study genotyped three risk variants: 8q24 (rs10505477: T >C and rs6983627: T >G) and 9p24 (rs719725: A >C) to analyze the association between each of the risk variants and CRC risk, but none of these variants were found to be associated with CRC risk in their study group.

It is important to determine the effects of genetic variation on individual gene expression and cell signaling pathways to understand slight perturbations at the molecular and cellular levels, thus going a long way in public health implications. It is also important to identify populations at higher risk of CRC for genetic stratification of subjects. Improved genetic surveillance programs will help to predict risk of CRC at the level of genotypes within populations. Studies of gene–environmental interactions may help provide plausible explanations to disease variance within treatment groups and overall disease risks. It is important to understand that role of GWAS in especially Arab world will provide important clues and can have high predictive values.

Recently, a new consortium called COlorectal cancer GENeTics (COGENT)[18] has been established for enhancing rigorous research in many countries. This consortium includes research groups from Europe, Australia, the Americas, China, and Japan actively working on CRC genetics. The consortium has recommended that Saudi Arabia takes part in this consortium and specifically work toward better understanding of CRC-related low-penetrance alleles in this population. Using GWAS tagging SNPs (tagSNPs) new, independent CRC predisposition SNPs close to BMP4 (rs1957636) and BMP2 (rs4813802) and near GREM1 between tagSNP rs4779584 were found to be associated with CRC risk. This technique used genetic fine-mapping studies through tagSNP with more than one functional SNP.[30]

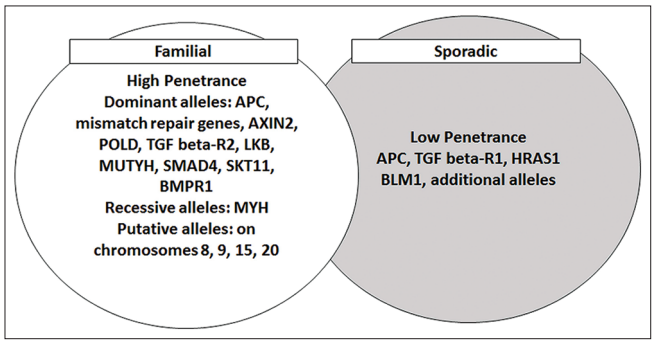

Figure 1: Familial and sporadic alleles with a risk for colorectal cancer

Early detection and appropriate prevention by excision of nonmalignant polyps has been found to reduce mortality and thus improve survival rates in subjects with CRC.[31] In addition, subjects who have been classified by genetic surveillance as low, moderate, and high-risk groups could also be prognostically taken care of through disease prevention programs.[32,33]

Scenario in the Kingdom of Saudi Arabia

According to Globocan, in Saudi Arabia, the number of cancer deaths are 9,100 in which CRC cancer incidences are 1168 (14.1%). It has been reported that in Saudi Arabia, the risk for colorectal cancer is low with a crude estimated incidence rate of 6 and a crude mortality rate of close to 4 as compared with the global estimates. The Globocan 2008 data reports an annual incidence rate of CRC of 14.3 per 100,000 men and 9.8 per 100,000 women with annual death rates of 10.1 in men and 6.9 in women.[23-38] A retrospective analyses conducted by Mosli and Alahwal[39] at the National Saudi Cancer Registry from 2001 to 2006 recorded an increasing

Table 2: Cancer susceptibility loci identified through GWAS in CRC

Locus/chromosome	SNP	Reference
8q24	rs10505477	Zanke *et al*.[20]
9p24	rs719725	Zanke *et al*.[20]
POU5F1P1, DQ515897, MYC	rs6983267	Tomlinson *et al*.[21]
18q21 *SMAD7*	rs4939827	Broderick *et al*.[22]
15q13 *CRAC1*	rs4779584	Jaeger *et al*.[23]
8q23.3 *EIF3H*	rs16892766	Tomlinson *et al*.[24]
10p14	rs10795668	Tomlinson *et al*.[24]
18q21 *SMAD7*	rs4939827	Tenesa *et al*.[25]
8q24	rs7014346	Tenesa *et al*.[25]
11q23	rs3802842	Tenesa *et al*.[25]
14q22.2 *BMP4*	rs4444235	Houlston *et al*.[26]
16q22.1 *CDH1*	rs9929218	Houlston *et al*.[26]
19q13.1*RHPN2*	rs10411210	Houlston *et al*.[26]
20p12.3	rs961253	Houlston *et al*.[26]
MLH1 promoter	rs1800734	Tomlinson *et al*.[27]
20p12 BMP2	rs4813802	Peters *et al*.[28]
5p33.15 *TERT-CLPTM1L*	rs2853668	Peters *et al*.[28]
1p33	rs12080929	Fernandez-Rozadilla *et al*.[29]
8p12	rs11987193	Fernandez-Rozadilla *et al*.[29]

GWAS: Genomewide association studies, CRC: Colorectal cancer, SNP: Single nucleotide polymorphism

incidence of CRC with a total of 4201 reported cases and a mean age of diagnosis being 58 years and slightly higher rates reported in males. Colon was the most common site of cancer followed by rectum. Approximately 23% subjects had localized disease, whereas 24% patients had distant metastasis at the time of diagnosis. The remaining patients presented with varying degrees of regional extension and/or an unknown stage of cancer. A study conducted by Isbister[40] that analyzed data from King Faisal Specialist Hospital and Research Centre Tumour registry reported the incidence of CRC below 40 years of age in Saudi Arabia—also suggesting that CRC is more aggressive in young age subjects with metastases being more common in older age subjects. Most importantly, there was an increasing incidence of CRC with lower age of diagnosis among Saudis necessitating the need for more stringent guidelines for CRC screening in this population. The clinical and pathological features of CRC in Saudi also mimic the Western population in terms of left-sided subsite dissemination and delayed appearance of the disease.[41]

An approach that can be used is presented in Figure 2. Tracking the genes and mutations that can influence CRC, identify variants and SNPs, sequencing and re-sequencing, and develop individual patient approaches for treatment through GWAS, all in larger patient populations is the best approach. It has also been shown that GWAS can identify germline mutations, but the genetic risk of adenomas for CRC has been presented in a latest study by Joshi *et al*. 2013 who have reported a probable association between the 1q31.1 locus and risk of advanced adenoma. This particular study also used an in silico analysis of GWAS data and observed the association of CRC susceptibility SNPs with adenoma risk [Figure 2].

In patients with chronic inflammatory bowel disease, a higher risk of CRC has been observed with risk increasing with family history, colitis, and severity of bowel inflammation. Therefore, early detection of CRC in these patients using molecular and genetic approaches, including DNA damage studies, changes in inflammatory mediators and oxidative stress have been proposed by Azer.[42] The geographic variations in CRC is influenced by diet as demonstrated by Nashar and Al-Murshed.[43] The study demonstrates that an increased consumption of meat and fat from animal sources could predispose an individual to an increased risk of CRC. It is therefore important to characterize as many biomarkers as possible to help in early detection of CRC. Also, biomarkers that serve as prognostic and diagnostic tools are essential in appropriate management of CRC. The development of multidrug resistance mechanisms has hindered the treatment strategies in colon cancer attributing to limited drug effects and overexpression of some oncogenes. The nonspecific action of P-gp in terms of their ability to distribute drugs to nontarget organs can cause decreased elimination and enhanced cytotoxicity of anticancer agents. This leads to initiation of studies that use gene silencing approaches for P-gp–mediated multidrug resistance. Binkhathlan and Alshamsan[44] have suggested that nanomedicine including inhibition by low molecular weight agents and RNAi technology can provide new avenues to eliminate or overcome drug resistance in cancer treatment. Defective glycosylation of galactosaminyltransferase enzymes have also been described to alter the pathology of many cancers. In silico analyses conducted on many genes that are involved in causing biochemical and molecular alterations in the etiology of cancers including colorectal cancers specific to the Saudi population may help in understanding cancers. In fact, in silico analyses of R297W-GALNT12 by researchers at King AbdulAziz University helped in the prediction of harmful effects and disruption of ionic interactions with consequent reduction of associated enzymatic activity reported in CRC.[45]

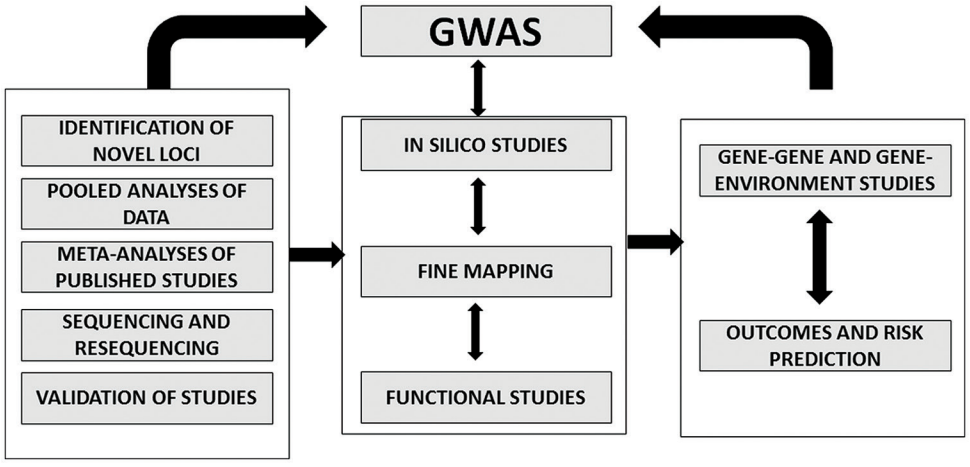

Figure 2: The role of genome-wide association studies (GWAS) in identifying the risk factors in a particular disease

Key concepts that need to be focused on, include the following

- Identifying new gene variants
- Understanding the physiological role of novel gene variants at the level of cells
- Developing diagnostic biomarkers for easy and early detection of CRC
- Understanding the association between different loci at the level of gene expression and its impact on the generation of pathophysiological processes
- Categorising risk alleles and their potential role in gene–gene and gene–environment interactions.

SUMMARY

GWAS have enhanced our understanding of the role of genetic variation in CRC risk and the possibility that target-specific drugs that suit a particular subject can be put forward for appropriate treatment by clinicians. GWAS specific to CRC have been performed in England, Scotland, and Canada. These studies recruited moderate sample sizes and provided very important results but also highlighted the need for many more such large scale population studies for the identification of new variants. Genetic population-based studies to identify new cancer predisposition genes through identification of low penetrance alleles in CRC are needed in Saudi Arabia. Published literature has so far confirmed the existence of at least 11 susceptibility loci; however, these are not enough for risk prediction necessitating the need for additional clinical studies in CRC in Saudi Arabia.

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