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Original article

Germline Variants in Patients with Sporadic Gastric Cancer from Southwestern Colombia

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Abstract

Introduction: Gastric cancer (GC) is a major public health problem worldwide, and Colombia is among the regions with the highest incidence. Multiple factors contribute to its development, including germline mutations (hereditary disease), which influence individual susceptibility. **Objective:** To identify germline variants in the exome of patients diagnosed with sporadic GC from regions of high and low incidence in Colombia. **Materials and methods:** Four blood samples were collected from patients with GC in the department of Nariño, Colombia, for whole-exome sequencing (WES). Bioinformatic analysis included raw data quality control, alignment of reads to the human reference genome, variant calling, annotation, filtering and prioritization, data visualization, and functional pathway analysis of genes harboring deleterious variants. **Results:** A total of 1,800,145 germline variants were identified in the analyzed patients. Five of these variants were reported in ClinVar as pathogenic, and these genetic alterations have not been previously described in patients with GC. The variants were identified in the genes *ACADS* (rs57443665), *BRCA1* (rs55688530), *FLNC* (rs200502811), *MCCC2* (rs757052602), and *ACSS2* (rs59088485), which have been previously reported and studied by The Cancer Genome Atlas (TCGA). **Conclusions:** Rare pathogenic molecular variants associated with susceptibility to GC were identified. Further studies are encouraged to validate these findings.

Keywords

Neoplasms; germline mutation; exome sequencing; genetic variation.

INTRODUCTION

Gastric cancer (GC) is the fifth most common type of cancer worldwide and one of the leading causes of cancer-related mortality, with approximately 968,000 new cases and more than 660,000 deaths estimated in 2022[(1)]. In Colombia, this neoplasm represents a major public health problem and ranks among the leading causes of cancer mortality, with an estimated mortality rate of 9.9 deaths per 100,000 inhabitants. Likewise, GC is among the neoplasms with the greatest disease burden in the country, with an approximate incidence rate of 12.8 new cases per 100,000 inhabitants[(1)]. However, the risk and incidence of GC are higher in certain regions of the country, such as the Andean region, where incidence rates reach 26.1 and 14.8 cases per 100,000 inhabitants in men and women, respectively[(2,3)].

The development of the disease can be explained by the interaction of multiple risk factors, including environmental factors, chronic infection with the bacterium *Helicobacter pylori*, diet, alcohol consumption, smoking, socioeconomic conditions, genetic factors, the presence of molecular

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variants, and epigenetic alterations, all of which together play a predominant role in the pathophysiology of GC[4].

In recent years, the search for molecular variants in different genes has intensified through the use of next-generation sequencing (NGS) technologies[4]. These high-throughput technologies enable the detection of genetic alterations associated with an increased risk of disease development[5,6]; however, sequencing may focus exclusively on protein-coding regions of the genome, given that approximately 85% of cancer-causing mutations are estimated to occur within coding regions. The technology used to analyze genetic alterations in coding regions is known as whole-exome sequencing (WES)[6–8].

Using whole-genome and whole-exome sequencing data, together with bioinformatic analyses, it has been possible to detect both somatic and germline genetic variants[9]. The latter have been less extensively studied and have been identified in approximately 10% of sporadic cancer cases; nevertheless, this type of mutation often goes unnoticed[10–12]. These mutations may interact at different stages of cancer development, acting synergistically to promote disease progression[13,14]. Furthermore, studying the interaction among cancer-associated germline variants provides deeper insight into aberrant pathways that may constitute potential therapeutic targets[15].

Therefore, the aim of this study was to characterize germline genetic variants in the exome of patients diagnosed with sporadic gastric cancer from two regions of high and low incidence in Colombia.

MATERIALS AND METHODS

Study Type

A quantitative, observational, and analytical study was conducted using available whole-exome sequencing data from patients with a histopathological diagnosis of GC.

Patients and Samples

Four Colombian patients older than 18 years with a histopathological diagnosis of intestinal-type GC were included. All patients had no family history of GC, tested negative for *H. pylori* infection, and had no comorbidities associated with other types of cancer or HIV infection. Blood samples were obtained by venipuncture under aseptic and fasting conditions. Sample collection was performed by healthcare professionals.

Genomic DNA Extraction

DNA was isolated using the DNA Isolation Kit Ultra Clean Blood Spin (MOBIO, Mobio Technologies Inc., San Diego, United States). DNA quantity and quality were determined quantitatively and qualitatively using the NanoDrop-2000 system and electrophoresis.

Whole-Exome Sequencing

Library enrichment for the capture of coding regions was performed using the Agilent SureSelect V5 kit. Sequencing of exonic regions was carried out on the Illumina HiSeq 2500 platform with 100–150 bp paired-end reads and 100× coverage. Raw sequencing data were obtained in FASTQ format, which includes read quality scores according to the Phred scale. Raw data quality was assessed using FastQC[16].

Low-quality sequence filtering and adapter trimming were performed using the BBMap package[17]. Reads were aligned to the human reference genome hg19/NCBI using the Burrows-Wheeler Aligner (BWA) software version 0.7.17, with the BWA-MEM algorithm and default parameters[18]. Alignment files were processed using SAMtools[19]. As part of the post-alignment processing, PCR duplicates were marked using the Picard MarkDuplicates.jar tool and removed from subsequent analyses (Broad Institute, Cambridge, Massachusetts).

Variant calling was performed using two programs:

- The "HaplotypeCaller" module from GATK (Broad Institute, Cambridge, Massachusetts), which simultaneously identifies germline SNPs and INDELs through local *de novo* haplotype assembly in active regions[20,21].
- FreeBayes, a complementary program based on a Bayesian model for SNP and INDEL detection. FreeBayes is haplotype-based and uses short-read alignments together with a reference genome to determine the most probable genotype combinations in the analyzed samples[22].

The hard filters recommended by the Broad Institute for SNPs and INDELs were applied to reduce false positives in the initial set of variants detected by HaplotypeCaller. These filters use properties or statistics describing, for each variant, the sequence context surrounding the variant site, the number of reads covering the site, the number of reads per allele, the proportion of reads in forward and reverse orientation, among other parameters. The raw set of variants generated with FreeBayes was filtered using the vcffilter tool with a quality score greater than 20.

The variants obtained by both algorithms were merged into a single file. Variant annotation was performed using the ANNOVAR software[23]. Subsequently, a filtering cascade was applied to prioritize variants potentially involved in the etiology of GC:

- Nonsynonymous exonic variants, variants involving gain or loss of the start or stop codon, and frameshift variants.

- Rare variants (MAF <0.01) according to the ExAC database[24].
- Single-nucleotide variants predicted to be deleterious according to SIFT[25] and MutationTaster[26].
- INDELs with high or moderate impact on protein coding according to SnpEff[27].
- Clinical significance information reported in ClinVar[28] and allelic frequencies across different populations according to the 1000 Genomes Project[29].

Subsequently, functional enrichment analysis was performed using the genes containing prioritized single-nucleotide variants through the DAVID 6.8 annotation database[30], employing the updated Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) databases.

Statistical Analysis

Statistical analysis was performed using licensed SPSS Statistics v27 software. A univariate descriptive analysis was conducted for the sociodemographic variables sex and age. In addition, a frequency distribution was established to determine the absolute frequency, defined as the total number of times a variant was repeated. A bar graph was generated to show the number of SNPs and INDELs with functional relevance within the exome of patients with GC.

Ethical Considerations

The study was approved by the Bioethics Subcommittee (INV 2084-I), under Approval Certificate No. SCBE06-17.

RESULTS

Four exomes from individuals without *H. pylori* infection diagnosed with intestinal-type GC were analyzed: three men and one woman, with an age range between 54 and 79 years and a mean age of 64 years (**Table 1**).

Table 1. Sociodemographic and Clinical Information of the Study Patients

n	ID	Sex/ Age	Diagnosis Lauren/de Borrmann Classifications	Access Number
1	SP03	M/79	Intestinal-type gastric cancer/Type 0	SAMN20956683
2	SP05	M/54	Intestinal-type gastric cancer/Type 0	SAMN20956684
3	SP06	F/62	Intestinal-type gastric cancer/Type V	SAMN20956685
4	SP07	M/63	Intestinal-type gastric cancer/Type V	SAMN20956686

F: female; M: male. Author's own research.

Between 42 and 69 million paired-end sequencing reads were obtained; sample SP03 showed the highest number of reads, with a total of 69,534,672. High sequencing quality scores were obtained, and more than 99% of the reads from all samples mapped to the human reference genome (hg19) (**Table 2**).

Table 2. Sequencing Quality Scores and Alignment Statistics

n	ID	Total Reads	Q30 (%)	Average Read Quality	Duplication (%)	Mapped Reads (%)
1	SP03	69.534.672	93.1	Q40	8.8	99.90
2	SP05	51.400.046	95.5	Q36	9.0	99.94
3	SP06	50.193.962	95.3	Q36	8.5	99.93
4	SP07	42.933.884	95.5	Q36	8.0	99.93

Author's own research.

Germline Variants in Gastric Cancer

A total of 1,800,141 germline variants were identified across the four exomes from patients with GC. Of these, 101,902 corresponded to coding regions (5.7%); 40,130 were nonsynonymous SNPs (39.4%), 230 were stop codon gain or loss variants (0.6%), and 1,783 were INDELs (4.4%). **Table 3** shows the frequency of SNPs and INDELs by variant type within the exonic region in the four samples analyzed.

During prioritization, germline variants were filtered by selecting only exonic variants with a frequency below 1% and classified as deleterious. Genes harboring these prioritized variants were considered for the functional enrichment analysis (**Figure 1**).

Biological Pathways Involved in Gastric Cancer

A total of 630 genes were included in the functional analysis. Functional pathways involving genes with deleterious variants revealed 20 significant biological pathways with p <0.05 (**Figure 2**). Likewise, five genes of biological relevance (*BRCA1*, ACADS, FLNC, ACSS2, and MCCC2) were prioritized, as they harbored single-nucleotide variants with clinically significant pathogenicity according to the ClinVar database (**Table 4**).

Mutations in the BRCA1 (rs55688530) and ACADS (rs57443665) genes were identified in sample SP03 from a patient originating from a coastal region of Colombia. According to the 1000 Genomes Project database, these two molecular variants have previously been reported in

the African population, with frequencies of 0.01 and 0.008, respectively.

Patient SP07, from an Andean region of Colombia, presented three variants: FLNC (rs200502811), previously reported in African (C: 0.009) and American (C: 0.001) populations; and ACSS2 (rs59088485) (C: 0.016) and MCCC2 (rs757052602) (T: 0.003), which have been reported exclusively in the American population (**Table 4**).

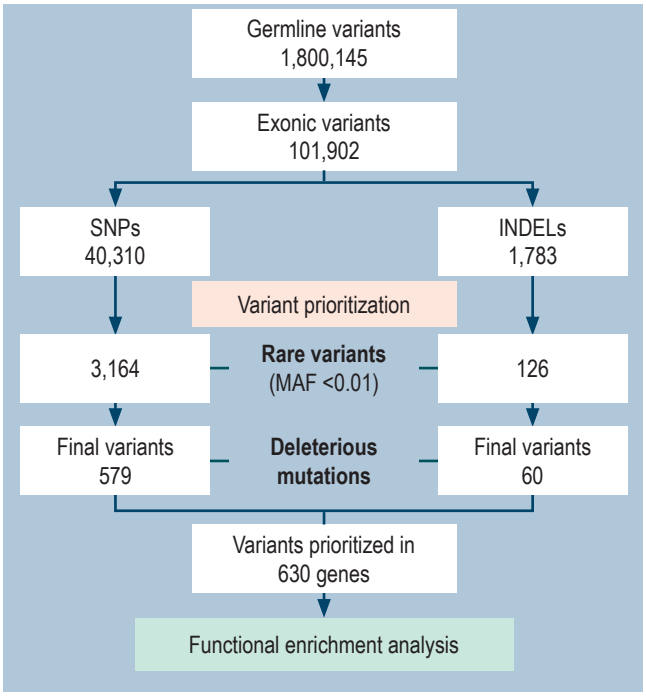


Figure 1. Workflow for the identification and prioritization of germline variants from whole-exome sequencing data of four patients with gastric cancer. Author's file.

DISCUSSION

GC is a complex and heterogeneous disease with high incidence and mortality rates, representing a serious threat to affected patients. Therefore, identifying relevant biomarkers for the diagnostic and prognostic assessment of the disease is essential[31,32].

In the present study, the results of the GO enrichment analysis showed that the genes were mainly associated with pathways previously described in GC, such as oxidation-reduction processes, the Wnt signaling pathway, sensory perception of sound, and endocytosis (**Figure 2**). An imbalance in the oxidation-reduction process may generate excessive levels of reactive oxygen species (ROS), which directly react with nucleic acids, causing both mitochondrial and nuclear genomic instability, thereby promoting carcinogenesis[33]. Wnt signaling regulates cell proliferation, differentiation, migration, and pluripotency; however, hypo- or hyperactivation of this pathway due to genetic alterations has been shown to promote the development of multiple solid tumors, including GC[34]. Endocytosis, in turn, plays an important role in the regulation of tumor metastasis[35]. KEGG pathway analysis showed that the genes were mainly enriched in glycolysis/gluconeogenesis, butanoate metabolism, and fructose and mannose metabolism (**Figure 2**), metabolic pathways that may be crucial in cancer research[36-38].

Furthermore, this study identified germline variants reported in ClinVar with clinically significant pathogenicity. These single-nucleotide variants had not previously been reported in patients with GC and were identified in the BRCA1, ACADS, FLNC, MCCC2, and ACSS2 genes (**Table 5**), which have already been described and stu-

Table 3. Frequency of Germline Alterations Identified by Whole-Exome Sequencing in Four Patients with Gastric Cancer

Sample	Intronic	Intergenic	Exonic	SNVs*			INDELs		
				Non-synonymous	Stop Codon Gain	Stop Codon Loss	Frameshift Substitution	Frameshift Deletion	Frameshift Insertion
SP03	194,300	162,423	28,321	10,042	87	22	9	150	186
SP05	274,587	322,622	24,337	10,076	100	12	9	144	117
SP06	262,971	300,106	24,528	10,078	101	13	5	130	80
SP07	233,732	244,789	24,716	10,116	87	14	9	126	98

*Includes mutations and polymorphisms. Author's own research.

Table 4. Reported Pathogenic Alterations and Their Frequency in Different Geographic Regions

Gene	Nucleotide Change	RefSNP	ClinVar	Allelic Frequency — 1000 Genomes
BRCA1	C → T	rs55688530	Conflicting interpretations of pathogenicity	Africa: T = 0.01
ACADS	T → C	rs57443665	Pathogenic/likely pathogenic	Africa: C = 0.008
FLNC	T → C	rs200502811	Conflicting interpretations of pathogenicity	Africa: C = 0.009 — America C = 0.001
ACSS2	T → C	rs59088485	Pathogenic	America: C = 0.016
MCCC2	A → T	rs757052602	Pathogenic/likely pathogenic	America: T = 0.003

Author's own research.

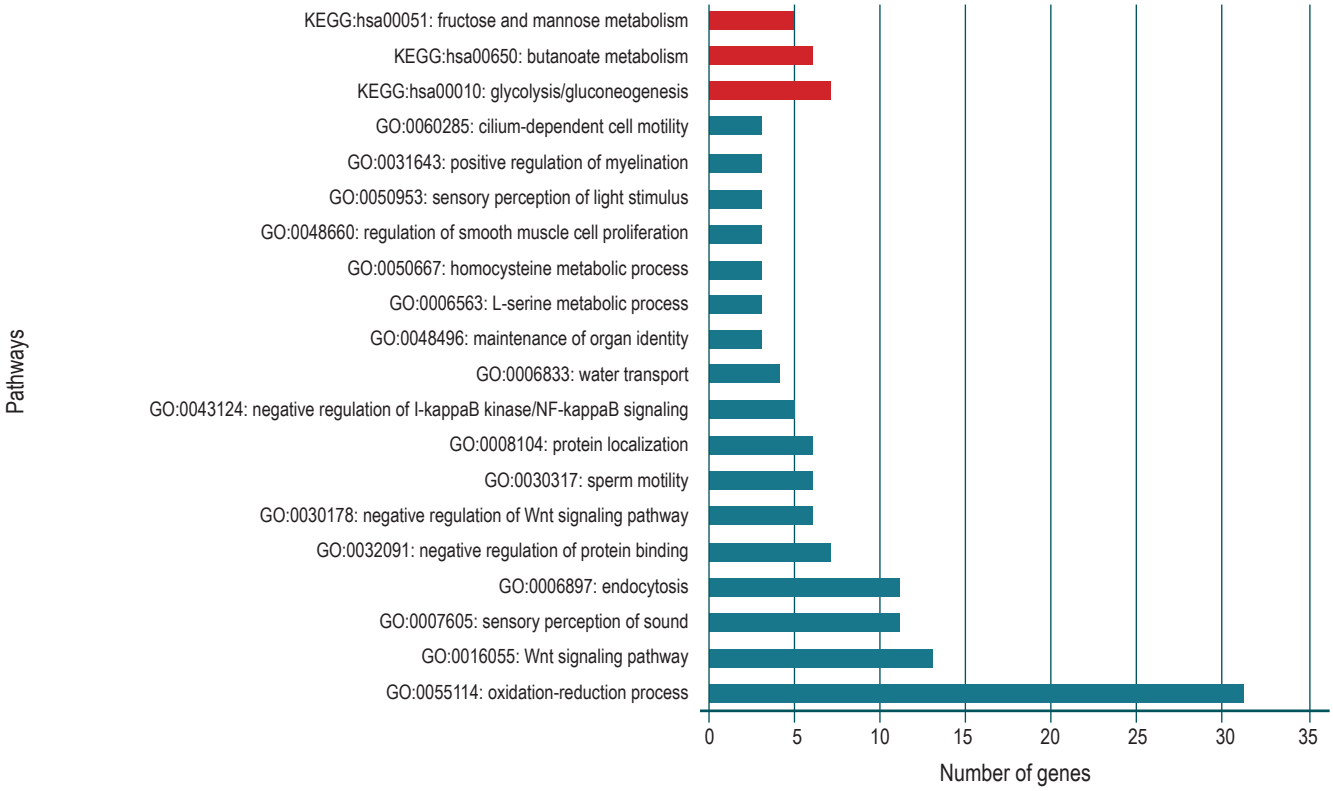


Figure 2. Biological processes (GO) and mutated KEGG pathways in patients with gastric cancer ($p < 0.05$, Fisher's exact test). Author's file.

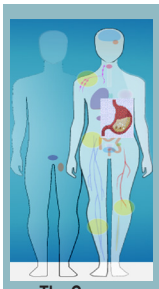
died within the framework of The Cancer Genome Atlas (TCGA) cancer genomics program[39].

The breast cancer 1 (BRCA1) gene plays a fundamental role in DNA repair as a cell-cycle checkpoint and functions as a regulator of epithelial cell growth[38]. Kim and collaborators[39] explained that carriers of germline BRCA1 mutations may have a four- to sevenfold increased risk of developing GC compared with the general population.

Regarding the ACADS gene, no reports of cancer-associated variants have been described; however, based on our findings, further investigation into the role of the rs57443665 variant is recommended, since according to ClinVar its significance is classified as pathogenic/likely pathogenic. In addition, this gene participates in the butanoate metabolic pathway. Han and colleagues[40] reported that this pathway could be crucial in cancer research, given

that butyrate inhibits histone deacetylases, thereby increasing the expression of genes that slow the cell cycle and induce apoptosis.

Table 5. Data on the Studied Genes Reported in The Cancer Genome Atlas



Gene	Cases by Sex		Vital Status		SNVs
	Male	Female	Alive	Deceased	
BRCA1	40	16	27	29	16
ACADS	29	8	22	15	16
FLNC	15	13	13	14	16
ACSS2	21	9	18	12	16
MCCC2	34	13	31	16	16

SNV: single-nucleotide variants. Adapted from: Kim H and colleagues. Oncol Lett. 2019;17(5):4383-92[39].

The FLNC gene encodes an actin-binding protein and has been reported by Slavin and collegues[41] as a candidate gene in GC research due to the presence of specific variants in a patient with the disease. The present study may support the conclusions of Slavin and colleagues[41], since the rs200502811 variant was identified in patients with GC with a deleterious prediction for protein coding and clinically significant pathogenicity according to ClinVar. This gene is part of the proteoglycan pathway in cancer, which is associated with cell proliferation, adhesion, angiogenesis, and metastasis[42].

With respect to the MCCC2 gene, this is the first report of a pathogenic variant (rs757052602) in a patient with GC. Caltabiano and colleagues[43] pointed out that few studies have associated MCCC2 with cancer; however, the authors identified that the gene is overexpressed in prostate cancer tumor tissues.

The ACSS2 gene has not been reported in GC studies or in publications implementing whole-exome sequencing (WES), and Hur and collegues[44] indicated that its role in the pathology remains unknown. Nevertheless, further investigation of this gene is necessary, since in the present study the rs59088485 variant was reported as pathogenic according to ClinVar.

Another interesting aspect to consider is the report of these variants in other populations, suggesting that the ethnic origin of patient SP03 (coastal region) is African, whereas patient SP07 (mestizo ethnicity) presented variants registered in both African and American populations. Genetic variation in Latin American populations could be explained by the convergence of Europeans, Amerindians, and especially Africans during the colonization process, which led to extensive genetic heterogeneity[45].

CONCLUSIONS

The results provide novel variants for investigation that may be associated with the development of GC and could explain part of the genetic component of this disease. It is important to note that this was an exploratory study with preliminary results; therefore, confirmation of the findings through validation studies, replication in samples from other populations, and more in-depth functional experiments is recommended. The need to include unaffected controls in exome sequencing studies is also emphasized in order to compare samples and filter variants with a higher likelihood of being pathogenic and involved in the development of GC. This will allow more precise identification of the genetic variants contributing to disease risk. Furthermore, the active search for variants and determination of their clinical impact will enable healthcare professionals to provide appropriate genetic counseling that contributes to timely decision-making in favor of patient health.

Informed Consent

Patients were informed verbally and in writing about the objectives, protocols, and characteristics of the study, and only those who signed the informed consent form were included.

Conflict of Interest

The authors of this article declare that they have no conflicts of interest.

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Use of Artificial Intelligence

The authors of this article declare that no artificial intelligence-assisted technologies were used.

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