An investigation into the role of inherited CEACAM gene family variants and colorectal cancer risk

Anna L. W. Huskey1,2 and Nancy D. Merner1*

Abstract

Objective: This study was designed to determine if CEACAM mutations are associated with inherited risk of colorectal cancer. Recently, protein-truncating mutations in the CEACAM gene family were associated with inherited breast cancer risk. That discovery, along with aberrant expression of CEACAM genes in colorectal cancer tumors and that colorectal cancer and breast cancer share many risk factors, including genetics, inspired our team to search for inherited CEACAM mutations in colorectal cancer cases. Specifically utilizing The Cancer Genome Atlas (TCGA) blood-derived whole-exome sequencing data from the colorectal cancer cohort, rare protein-truncating variants and missense variants were investigated through single variant and aggregation analyses in European American and African American cases and compared to ethnic-matched controls.

Results: A total of 34 and 14 different CEACAM variants were identified in European American and African American colorectal cancer cases, respectively. Nine missense variants were individually associated with risk, two in African Americans and seven in European Americans. No identified protein-truncating variants were associated with CRC risk in either ethnicity. Gene family and gene-specific aggregation analyses did not yield any significant results.

Keywords: Colorectal cancer, CEACAM, TCGA, Inherited, Familial, Genetics, Genetic risk, Risk variant

Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in the US [1], and the lifetime risk of development is 4–5% [1, 2]. However, this risk can increase with many factors, including a family history of CRC [1]. Approximately 30% of CRC cases are familial [2, 3], and of those cases with a known genetic cause, the majority have Lynch syndrome [4]. However, up to 30% of familial cases are estimated to be genetically unsolved [5].

Attempting to discover new CRC genetic risk factors, herein, the CEACAM (Carcinoembryonic antigen-related cell adhesion molecule) gene family was investigated. CEACAM genes are a part of the Ig superfamily. These genes have diverse functions, including cell adhesion and signaling, influencing immunity, angiogenesis, and cancer [6–8]. Aberrant expression of CEACAM genes has long been associated with tumorigenesis, and atypical expression has been heavily linked to CRC development and progression [6, 8]. In 1965, CEA (more currently known as CEACAM5) was first identified as a tumor marker for CRC [9, 10]. Additionally, CEACAM6 is overexpressed in CRC and has been determined to increase invasiveness [11]. Contrarily, CEACAM1 [12, 13] and CEACAM7 [14] have decreased expression in CRC. Furthermore, somatic mutations in CEACAM1 [13] and CEACAM5 [15] have been detected in CRC tumors. Nonetheless, the impact of inherited CEACAM gene mutations on CRC risk has yet to be determined.
Recently, rare protein-truncating variants (PTVs) in the CEACAM gene family were associated with the inherited risk of breast cancer [16]. That discovery, along with aberrant expression of CEACAM genes in CRC tumors and that CRC and breast cancer share many risk factors, including genetics [1, 17, 18], inspired our team to determine if CEACAM mutations are associated with CRC inherited risk.

Main text

Methods

Blood-derived exomes of CRC cases in The Cancer Genome Atlas (TCGA) were analyzed to investigate if CEACAM mutations play a role in inherited risk. Through approved research project #10805, whole-exome binary sequence alignment mapping (BAM) files were downloaded from the Genomic Data Commons (GDC) Data Portal Repository. Samples were acquired by setting specific filters. Filters under the ‘Cases’ category included Project (TCGA-COAD), Samples Sample Type (Blood-Derived Normal), and Race (‘Black or African American’ and ‘White’). The samples were further filtered under the ‘Files’ category, including Experimental Strategy (WXS) and Data Format (BAM). A total of 48 sample files were obtained for African Americans and 199 for European Americans. These files were downloaded using the GDC Data Transfer Tool (version 1.2.0).

The downloaded BAM files, which had previously been aligned to the hg38 human reference genome, were processed using the remaining portions of a pipeline adapted from the Genome Analysis Toolkit’s (GATK’s) best practices pipeline [19]. Base quality scores were recalibrated using BaseRecalibrator. Following base recalibration, the BAM files underwent coverage calculations for the exome and each CEACAM gene. Samtools depth function [20, 21] was used to determine the exome coverage using a BED file generated from UCSC Table Browser with the specifications: clade (Mammal), genome (Human), assembly (Dec. 2013 (GRCH38/hg38), group (Genes and Gene Predictions), track (NCBI RefSeq), and table (UCSC RefSeq (refGene)) with genome as the (Genes and Gene Predictions), track (NCBI RefSeq), (Human), assembly (Dec. 2013 (GRCH38/hg38), group with the specifications: clade (Mammal), genome using a BED file generated from UCSC Table Browser including genetics [1, 17, 18], inspired our team to determine if CEACAM and breast cancer share many risk factors, including genetics [1, 17, 18], inspired our team to determine if CEACAM mutations are associated with CRC inherited risk.

The whole-exome BAM files downloaded from TCGA had an average exome coverage of 8X, ranging from 2.3X to 21.4X among the samples. Coverage values were also generated for each CEACAM gene (Additional file 1: Table S1). The average coverage for the gene family was 22.9X, with 100% of the bases covered at least 1X (Additional file 1: Table S1).

After filtering for rare PTVs and missense variants in the entire CEACAM gene family within the TCGA CRC cohort, a total of 14 different variants were identified in African American cases (one frameshift and 13 missense; Additional file 2: Table S2), and 34 different variants were identified in European American cases (one frameshift, two splice, and 31 missense; Additional file 3: Table S3). All identified variants were heterozygous, and there were
no cases of compound heterozygosity. The average coverage for the 14 variants identified in African Americans was 49X, ranging from 19 to 423X. Similarly, the average coverage for the 34 variants detected in European Americans was 42X, ranging from 3 to 923X. No identified PTVs were associated with CRC risk in either ethnicity. In African American cases, five of the 13 missense variants were classified as probably damaging; however, none of those mutations were associated with CRC risk. Only two variants were determined to be individually associated with African American CRC risk, including CEACAM3:p.(Y95N) and CEACAM8:p.(T247A), both predicted to be likely benign (Table 1).

In European American cases, 10 of the 31 missense variants were predicted to be probably damaging, but only two of which were found to be associated with CRC risk, CEACAM1:p.(Y68C) and CEACAM18:p.(C357G). A total of seven variants were determined to be individually associated with CRC in European Americans, all of which were missense variants, including the two aforementioned probably damaging missense variants and five predicted to be benign (Table 2).

Gene family and gene-specific aggregation analyses did not yield any significant results, including a combined assessment of PTVs, missense mutations, and probably damaging missense mutations.

Discussion

Upon surveying the CEACAM gene family for rare PTVs and missense variants in CRC cases from TCGA and controls from the EVS, no gene-based or gene family-based associations with inherited risk of CRC were revealed. These results were unexpected due to the previous association of rare PTVs in the CEACAM gene family with inherited breast cancer risk [16], the known similarities between breast cancer and CRC risk [1, 17, 18], and the dis-regulation of CEACAM genes in CRC tumors [6, 8–15]. Moreover, it has been demonstrated that CEACAM gene function can be affected by even minor genetic changes [27], and specific residues within CEACAM proteins are crucial for normal function [12, 30, 31].

Despite the lack of association from aggregation analyses, individual variants were associated with CRC inherited risk (Tables 1 and 2). All associations involved individual missense variants; none involved PTVs, unlike the association of CEACAM PTVs with breast cancer risk [16]. Only four different PTVs were detected amongst all CRC cases, none of which overlapped between ethnicities. In European American CRC cases, two splice variants

### Table 1 Significant rare mutations identified in TCGA CRC African American (AA) cohort

| Gene      | Chr 19 position | Mutation type | Functional prediction—polyphen | cDNA change | Protein change | TCGA AA Colon MAF (%) | EVS AA MAF (%) | AA individual P-values |
|-----------|-----------------|---------------|--------------------------------|-------------|----------------|------------------------|----------------|------------------------|
| CEACAM3:  | 41797807        | missense      | benign: 0.159                  | c.283T > A  | p.(Y95N)       | 5.208                  | 0.894          | 0.002                  |
| NM_0011815|                 |               |                                |             |                |                        |                |                        |
| CEACAM8:  | 42589003        | missense      | benign: 0.001                  | c.739A > G  | p.(T247A)      | 4.167                  | 0.931          | 0.015                  |
| NM_0011816|                 |               |                                |             |                |                        |                |                        |

### Table 2 Significant rare mutations identified in TCGA CRC European American (EA) cohort

| Gene      | Chr 19 position | Mutation type | Functional prediction—polyphen | cDNA change | Protein change | TCGA EA colon MAF (%) | EVS EA MAF (%) | EA individual P-values |
|-----------|-----------------|---------------|--------------------------------|-------------|----------------|------------------------|----------------|------------------------|
| CEACAM1:  | 42527262        | missense      | probably-damaging: 1.0         | c.203A > G  | p.(Y68C)       | 0.503                  | 0.070          | 0.046                  |
| NM_001184815|              |               |                                |             |                |                        |                |                        |
| CEACAM4:  | 41625657        | missense      | benign: 0.325                  | c.368G > A  | p.(R123E)      | 0.503                  | 0.000          | 0.002                  |
| NM_0011817|                 |               |                                |             |                |                        |                |                        |
| CEACAM8:  | 42589735        | missense      | benign: 0.005                  | c.425C > T  | p.(P142L)      | 0.503                  | 0.012          | 0.006                  |
| NM_0011816|                 |               |                                |             |                |                        |                |                        |
| CEACAM18: | 51483229        | missense      | probably-damaging: 1.0         | c.1069T > G | p.(C357G)      | 0.503                  | 0.059          | 0.036                  |
| NM_001080405|            |               |                                |             |                |                        |                |                        |
| CEACAM19: | 51483284        | missense      | benign: 0.013                  | c.1124A > G | p.(Q375R)      | 0.503                  | 0.059          | 0.036                  |
| NM_0020219|                 |               |                                |             |                |                        |                |                        |
| CEACAM20: | 44512936        | missense      | benign: 0.062                  | c.1445C > T | p.(T482I)      | 0.503                  | 0.000          | 0.002                  |
| NM_001102597|            |               |                                |             |                |                        |                |                        |
were detected, including \textit{CEACAM7}:c.64+1G>T and \textit{CEACAM21}:c.882+1G>A, and a frameshift mutation was detected, \textit{CEACAM20}:p.(F542Fs*56). One frameshift mutation was detected in an AA CRC case, \textit{CEACAM21}:p.(T32Pfs*47).

Overall, 9 missense variants were determined to be individually associated with risk, two in African Americans and seven in European Americans. Three associated variants were within the Ig V-set (variable) domain (Fig. 1), including \textit{CEACAM1}:p.(Y68C) and \textit{CEACAM4}:p.(R123E), which were associated with European American CRC risk, and \textit{CEACAM3}:p.(Y95N), which was associated with African American CRC risk (Fig. 1). The Ig V-set domain is crucial for the dimerization of many CEACAM proteins and their ability to function within normal ranges [31, 32]. In CEACAM1, mutating particular residues within the Ig V-set domain can affect the monomer-homodimer exchange and result in the protein staying in a monomeric state [31]. CEACAM1’s ability to dimerize is required for proper function [33–36]. Knowing that CEACAM1 dimerization is crucial and CEACAM1’s current role in CRC [12, 13], \textit{CEACAM1}:p.(Y68C) is a probable CRC inherited risk factor. \textit{CEACAM3}:p.(Y95N) has been reported as benign in ClinVar; however, limited information was provided for that clinical classification [37]. Considering \textit{CEACAM3} has potential links to CRC [38, 39], validating the association of \textit{CEACAM3}:p.(Y95N) with AA CRC inherited risk is crucial in identifying possible risk factors. Lastly, \textit{CEACAM4} has been previously associated with thyroid cancer [40], but its role in CRC is unknown. Missense variants within the Ig V-set domain identified in this study could result in repressed dimerization and require further investigation.

Two statistically significant missense variants were identified in both \textit{CEACAM8} and \textit{CEACAM18}. The two variants in \textit{CEACAM8}, p.(P142L) and p.(T247A), were associated with CRC risk in European American and African American cases, respectively, and occur between functional domains of the protein (Fig. 1). Even though the role of these variants is unclear, CEACAM8 forms dimers with CEACAM6 and CEACAM1 [32, 35], both of which have previous associations with CRC [11–13]. \textit{CEACAM18} p.(C357G) and p.(Q375R) were significantly associated in European American CRC, and p.(C357G) was predicted to be pathogenic through PolyPhen2 [27]. These mutations occur after known functional domains for CEACAM18 (Fig. 1) but could influence how the protein interacts with the cell membrane. Beyond these two \textit{CEACAM18} variant associations, there is no known link between CEACAM18 and CRC.

A single missense mutation in both \textit{CEACAM19} p.(R258T) and \textit{CEACAM20} p.(T482I) was associated with European American CRC. Both of these mutations occur within the cytoplasmic region of the protein but before the ITAM binding motifs (Fig. 1). The possible impacts of these mutations are unclear; however, \textit{CEACAM19} and \textit{-20} have previous cancer links [41–45]. Furthermore, \textit{CEACAM20} has been determined to play a role in gut microbiome regulation [46, 47]. The microbiome is known to influence CRC risk and progression [1], which could explain \textit{CEACAM20}'s role in CRC risk. Additionally, \textit{CEACAM} gene expression is altered in Inflammatory Bowel Disease (IBD)[38, 48], another well-established risk factor for CRC [49–51]. Exploring how \textit{CEACAM} mutations and aberrant expression result in both IBD and CRC is extremely important.

![Fig. 1](image_url) Domain analysis of the significant rare mutations identified in TCGA-COAD cohort
Unfortunately, IBD diagnoses were unavailable for TCGA CRC cases to explore that link.

Overall, this study aimed to determine if inherited CEACAM variants play a role in CRC risk. No gene- or gene family-based associations were identified, but nine individual missense variants in seven different CEACAM genes appear to be associated with inherited CRC risk. Further investigation is warranted.

**Limitations**

It is important to note that the TCGA CRC cohort is not a hereditary/familial CRC cohort. Though CEACAM variants do not appear to play a significant role in this cohort, studying hereditary/familial CRC cohorts could reveal different findings. Such investigations are important considering that a large percentage of inherited CRC is suspected to be influenced by lower penetrant variants compounded with environmental factors [1, 5]. Furthermore, the TCGA CRC cohort was subdivided by ethnicity, and European American cases were represented ~4X more than African American cases. This under-representation is a concerning limitation, as African Americans have the highest CRC incidence and mortality rates of all ethnicities in the United States [52]. Both TCGA CRC ethnic groups had a limited number of cases, and with the prevalence of previous research linking the CEACAM genes to spontaneous CRC [6, 8, 11–15, 38, 39, 53–55], more genetic and functional investigations of the CEACAM gene family should be carried out.

**Abbreviations**

AA: African American; BAM: Binary sequence alignment mapping; CRC: Colorectal cancer; ELM: Eukaryotic linear motif; EA: European American; EVS: Exome variant server; GATK’s: Genome analysis toolkit’s; gVCF: Genome variant calling format; GDC: Genomic data commons; MAFs: Minor allele frequencies; NHLBI: National Heart, Lung, and Blood Institute; PTVs: Protein-truncating variants; TCGA: The Cancer Genome Atlas.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s13104-022-05907-6.

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**Authors’ contributions**

ALWH and NDM wrote the manuscript. ALWH performed bioinformatic processing and statistical analyses. Both authors read and approved the final manuscript.

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**Availability of data and materials**

The datasets supporting the conclusions of this article are available in The Cancer Genome Atlas GDC data portal TCGA-COAD repository, https://portal.gdc.cancer.gov/projects/TCGA-COAD.

**Declarations**

**Ethics approval and consent to participate**

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki and have been approved by the Auburn University Institutional Review Board of the Office of Research Compliance (protocol #19-302 EP 1907). Furthermore, a request (#44682–1) for a Data Use Certification for TCGA data access was submitted and project (#10805) was approved. TCGA study participants provided informed consent through NIH-approved protocols.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Author details**

1Department of Pathobiology, College of Veterinary Medicine, Auburn University, 1130 Wire Road, Auburn, AL 36849, USA. 2Department of Drug Discovery and Development, Harrison School of Pharmacy, Auburn University, 3306 Walker Building, Auburn, AL 36849, USA.

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