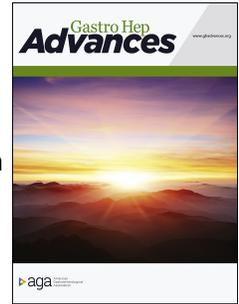# Journal Pre-proof

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Association of *CDH1* Germline Variants and Colon Polyp Phenotypes in Patients with Hereditary Diffuse Gastric Cancer

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Data Transparency Statement

Deidentified individual participant data that underlie the reported results will be made available 3 months after publication for a period of 5 years after the publication date. Proposals for access should be sent to jeremy.davis@nih.gov. The study protocol is included as a data supplement available with the online version of this article.

Ethical Statement

The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

ABSTRACT

Background and Aims: Germline *CDH1* variants resulting in E-cadherin loss of function result in an increased risk of diffuse type gastric cancer and lobular type breast cancer. However, the risk of developing other epithelial neoplasms, specifically colorectal cancer, is unknown.

Methods: Patients enrolled in a prospective natural history study of hereditary gastric cancer who underwent at least one colonoscopy were evaluated.

Results: Out of 300 patients with *CDH1* pathogenic or likely pathogenic variants, 85 underwent colonoscopy. More than half of patients (56%, 48/85) had at least one colorectal polyp. Most of those patients (83%, 40/48) had at least one precancerous polyp (adenoma or sessile serrated lesion). More than half (56%) of patients younger than age 45 had a colorectal polyp. Of those with polyps, the most frequent *CDH1* variant type was canonical splice site (27%, 13/48) followed by nonsense (21%, 10/48). There was no association between *CDH1* variant type and increased likelihood of colorectal polyps.

Conclusions: In summary, a majority of *CDH1* variant carriers who underwent colonoscopy had colorectal polyps detected, and most subjects were less than 45 years old. This study of colorectal cancer risk based on the prevalence of colorectal polyps in the *CDH1* population requires further investigation to appropriately counsel patients on colorectal cancer screening. Clinical trial registry website: https://clinicaltrials.gov/. Clinical trial number: NCT03030404

INTRODUCTION

Hereditary diffuse gastric cancer (HDGC) is a clinically defined cancer syndrome attributed to germline inactivating *CDH1* variants.[1] While this syndrome is commonly characterized by the early onset of diffuse gastric cancer (DGC) and lobular breast cancer (LBC), the clinical phenotype of HDGC demonstrates considerable heterogeneity with regard to cancer penetrance in families and the age of cancer onset.[2-4] Estimated lifetime risk of DGC is 24-42% and diagnosis of advanced DGC can occur as early as the second decade and throughout late adult life.[5, 6] Approximately 1-3% of incident gastric cancers are considered heritable, and CDH1 variants are implicated in up to 20% of hereditary diffuse gastric cancers.[3] Furthermore, variants in the *CDH1* gene have been implicated in other neoplastic processes.[7, 8] Loss of E-cadherin protein expression has been implicated in the progression of colorectal adenomas to carcinoma and variants in the *CDH1* gene are present in patient-derived colorectal cancer cell lines.[9] Reports of early onset colorectal cancer in HDGC families and cases of colorectal cancer in *CDH1* variant carriers raises questions about a predisposition to colorectal neoplasia in patients with germline *CDH1* variants.[10]

Despite advances in our understanding of germline *CDH1* variants, individuals with HDGC syndrome can have variable clinical presentation and histopathologic findings. Both gastric cancer and LBC are rare with an estimated 26,380 and 43,000 new cases in 2022, respectively.[11, 12] Hereditary causes of gastric cancer are expected to make up 1-3% of incident cases. This has contributed to challenges in counseling patients on the optimal timing to engage in cancer screening and, specifically,recommendations for risk-reducing total gastrectomy. Few data are available analyzing the progression from preclinical, indolent gastric lesions to widely invasive, aggressive phenotypes. Furthermore, the underlying mechanisms for variability in

clinical phenotypes and immunophenotypic profile have not been clearly defined.[13-18] Possible explanations include the specific *CDH1* genotype, the potential for certain variants to activate cryptic or alternative splice sites, and the mechanisms that drive biallelic *CDH1* loss or loss of heterozygosity. Purported genotype-phenotype associations in patients with germline *CDH1* variants have been severely limited by the diversity of *CDH1* genotypes and the limitations of comparisons in relatively small cohorts.[19] As with other hereditary conditions, genotype-guided cancer screening and surveillance would allow for individualized management of patients affected by this hereditary cancer syndrome.

At present there is insufficient evidence to recommend additional colorectal cancer screening beyond adherence to national population screening guidelines for patients with HDGC. However, expert opinion has included the proposal that colorectal cancer screening should be considered starting at age 40 in patients with *CDH1* pathogenic variants.[20] The primary aims of this study were threefold; to determine if *CDH1* pathogenic and likely pathogenic (PLP) variant carriers are at increased risk of colon polyps compared to the general population, to assess whether colon polyp risk at a young age is elevated in patients with *CDH1* PLP variants, and to identify genotype-phenotype correlations with colonic neoplasia.

METHODS

Patients with a confirmed *CDH1* PLP variant were enrolled in a hereditary gastric cancer study at the National Cancer Institute (Bethesda, MD; NCT NCT03030404) between January 2017 through April 2021. The study was approved by the National Institutes of Health Institutional Review Board and all patients provided written informed consent. All study participants were evaluated by a certified genetic counselor and a detailed family pedigree with

specific attention to cancer history was collected. Patients who underwent at least one confirmed colonoscopy at any time, and for any indication, were identified from the study database. Patient demographics, personal and family cancer histories, including colorectal cancer, were collected prospectively and reviewed or updated as part of this retrospective analysis. Colonoscopy procedure findings were recorded along with relevant surgical pathology results from each procedure. The histologic subtype of polyps that were biopsied was recorded. Among those individuals who underwent multiple colonoscopy procedures only the patient's first colonoscopy procedure was considered in an effort to standardize data ascertainment. Indication for the colonoscopy and age of patient at time of colonoscopy was recorded. Left sided colon polyps were defined as those located distal to the splenic flexure (i.e. descending colon, sigmoid, rectum), right sided colon polyps were defined as those proximal to the hepatic flexure (i.e. ascending colon, cecum), and the transverse colon was assigned its own category.

For this analysis, *CDH1* PLP variant carriers were categorized into one of two groups: those with colorectal polyps (CP) and those with no colorectal polyps (NCP). Descriptive statistics for demographic, clinical, endoscopic, and histologic covariates were described for the entire cohort and stratified by the two groups (CP and NCP). Statistically significant differences between categorical ordinal variables was performed using Pearson's chi-square test whereas Fischer's exact 2-sample T-test was used for categorical continuous variables. Univariate logistic regression analysis using a chi-square test was also performed to identify variables associated with an increased odds for the presence of colorectal polyps. Logistic regression analysis was additionally performed to evaluate for any association between *CDH1* variant type/domain and presence of colorectal polyps, presence of multiple colorectal polyps and presence of precancerous colorectal polyps, and clinicopathologic variables predictive of colorectal polyp

location. Finally, logistic regression analysis was performed to identify any association between *CDH1* PLP variant type and a family history of colorectal cancer. All models estimated the odds ratio (OR) and 95% confidence intervals (CI) with 2-sided P-value of <0.05 as considered statistically significant. All analyses were conducted using STATA 15 (StataCorp, LLC) (College Station, TX).

All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

3.1. Clinical and Genotype Characteristics of Study Cohort

Among 300 patients with confirmed *CDH1* PLP variants who enrolled in a prospective study of hereditary gastric cancer between January 2017 and April 2021, a colonoscopy was performed in 85 patients from 58 unique families (Figure 1). In most patients (97%, 83/85) colonoscopy was performed for colorectal cancer screening or surveillance purposes. The majority of patients were non-Hispanic White (98%) and female (61%) with an average age of 54 years (range 23-73) and mean BMI of 28.5 kg/m^2 (Table 1). Most patients (80%) had a family history of gastric cancer and a family history of breast cancer (73% in any relative; 48% in a first degree relative). Splice spite (canonical) variants were the most frequent *CDH1* variant among patients with family histories of colorectal cancer (12/30, 40%), gastric cancer (21/67, 31.3%) and breast cancer (24/62, 38.7%) (Supplemental Table 1A). On logistic regression analysis, none of the *CDH1* mutation types were significantly associated with an increased odds for a family history of colorectal cancer (P>0.05 for all) (Supplemental Table 1B) Among those patients (37/85, 43%) who elected to undergo prophylactic total gastrectomy, signet ring cell carcinoma was identified in nearly all (95%).

Among this cohort of patients undergoing colonoscopy for any indication, 48 patients (56%) had at least one colorectal polyp and 37 (44%) had no colorectal polyps detected (Figure 2). More patients in the NCP group had a family history of breast cancer (86.5% vs 62.5%, P=0.02), and 22% of patients had a personal history of breast cancer. One female patient in our study had a personal history of colorectal cancer diagnosed at the age of 69, and 35% (30/85) individuals had a family history of colorectal cancer, the majority (80%, 24/30) of whom had a first- or second-degree family member affected. Splice site (canonical) variants were most the most frequent (31%, 26/85) *CDH1* variant type overall. While gene deletions appeared more frequently in the CP group (23%, 11/48 vs 5%, 2/37), there was no difference in *CDH1* variant type between CP and NCP groups (p=0.27) and there were no differences between the CP and NCP groups with regard to *CDH1* domain affected (p=0.97) (Table 2).

3.2. Frequency of Colorectal Polyps Among Carriers of CDH1 PLP Variants

Forty-eight (56%, 48/85) patients were found to have at least one polyp at the time of colonoscopy. Data was available on 35 of them. The mean number of polyps detected at colonoscopy was 1.35 ± 0.55 (range: 0-7 polyps). Among individuals who harbored any colorectal polyp (CP), most (83%, 40/48) had at least one precancerous polyp, 41% (36/48) had at least one adenomatous polyp, and 5% (4/48) harbored at least one sessile serrated lesion. In addition, 23% (11/48) of patients harbored at least one hyperplastic polyp. The frequency of preneoplastic polyps was similar in females (46%, 25/54) and males (48%, 15/31) (p=0.85). Most patients with colorectal polyps harbored left sided colorectal polyps (52%, 25/48) (Figure 3). There were no independent predictors associated with increased odds of right-sided, left-sided, or transverse colon polyps (p>0.05 for all).

3.3. Prevalence of CDH1 PLP Patients with Colorectal Polyps at a Younger Age

We stratified patients into those younger than the age of 45 (19%, 16/85) and aged 45 or older (81%, 69/85) to assess whether *CDH1* PLP carriers harbor colorectal polyps and preneoplastic polyps at a younger age. This age cutoff was based on United States Preventive Services Task Force updated guidelines for colon cancer screening in adults. Among our study cohort, 56.3% of *CDH1* PLP variant carriers younger than 45 years old harbored colorectal polyps and 55.7% of *CDH1* PLP variant carriers 45 years and older harbored colorectal polyps. There was no statistically significant difference with regard to presence of colorectal polyps when comparing patients younger than and older than 45 years (P=0.97). 50% of *CDH1* PLP variant carriers younger than 45 years harbored preneoplastic lesions whereas 45.7% of patients older than 45 years harbored preneoplastic lesions. Similar to colorectal polyps overall, there was no statistically significant difference with regards to prevalence of preneoplastic colorectal polyps when comparing *CDH1* PLP variant carriers <45 years and those ≥45 years old (P=0.92) (Figure 4).

The majority of *CDH1* PLP variant carriers were in their fifth and sixth decade of life, whereas a small proportion of patients were in their second and seventh decade. None of the patients undergoing a colonoscopy in their twenties were found to harbor polyps. However, the majority of patients younger than 50 undergoing colonoscopy (16/26, 61.5%) harbored at least one colorectal polyp. Furthermore, the highest prevalence of colorectal polyps overall were identified in those patients undergoing colonoscopies in their fourth decade of life (9/12, 75%), whereas the highest prevalence of precancerous colorectal polyps were among those individuals in their seventh decade (3/3, 100%) (Figure 6). There was no statistically significant difference in

prevalence of colorectal polyps overall when stratified by patient's decade of age (P=0.62), nor was there a statistically significant difference detected in the prevalence of pre-cancerous colorectal polyps (P=0.74). A demonstration of age at colonoscopy corresponding to *CDH1* variant type and polyp type is provided (Supplemental Figure 1).

3.4. Genotype-Phenotype Correlation between CDH1 Variants and Colorectal Polyp Detection

A splice site (canonical) *CDH1* gene variant was among the most frequent variant types (30%, 26/85) followed by nonsense variants (22%, 19/85). The cadherin domain was the most frequently affected *CDH1* gene domain overall (54%, 38/70) (Table 2). Colorectal polyps were most prevalent among individuals with a splice site (canonical) gene variant (27%, 13/48). Similarly, individuals with splice site variants had the highest prevalence of precancerous colorectal polyps (39%, 7/18) compared with other variant types. When stratified by *CDH1* variant type, there was no difference in the prevalence of colorectal polyps overall (P=0.27) or the prevalence of precancerous polyps (P=0.44) (Figure 7). Splice site variants were the only variant type associated with an increased likelihood for the presence of polyps overall (OR 7.93, 95% CI 1.48, 8.82; P=0.02). Both nonsense and splice site *CDH1* variants were associated with increased odds of harboring multiple (>1) colorectal polyps (OR 1.88, 95% CI 0.26, 3.49 and OR 1.93, 95% CI 0.35, 3.50, respectively; P=0.02 for both). There was no association between *CDH1* variant type and increased likelihood of precancerous colorectal polyps (P>0.05 for all) (Figure 7).

DISCUSSION

In this large, prospective cohort study of *CDH1* PLP variant carriers who underwent colonoscopy, we observed that more than half of individuals harbored at least one colorectal polyp. Remarkably, many patients who had colorectal polyps were younger than 45 years and a majority harbored a preneoplastic colorectal polyp. Furthermore, a sizeable proportion of *CDH1* variant carriers had a family history of colorectal cancer in a first degree or second degree relative. Our analysis revealed that splice site (canonical) and nonsense variant types were associated with a higher risk for presence of colorectal polyps, suggesting a possible association between *CDH1* genotype and colon disease risk. To our knowledge, this is the largest study on colonoscopy findings among patients with germline *CDH1* variants to date. Although it has been postulated that colorectal carcinomas may constitute part of the HDGC disease spectrum, until now, data have been limited on colonoscopy findings in this patient population, specifically colorectal polyps. Colorectal carcinoma commonly develops as part of the progression of adenomatous polyps which is why early diagnosis has resulted in improved survival rates in recent decades.[12] In the current study of 85 adult *CDH1* variant carriers, 56% had at least one colorectal polyp and 41% of those were adenomatous. In the U.S. it is estimated that at least 25% of men and 15% of women undergoing screening colonoscopy will have one or more adenomatous polyps. Assuming an adenoma detection rate of 25%, the average number of endoscopically detected polyps per procedure would be 1.1 polyps.[21] Notably, the adenoma detection rate in our study is nearly double the expected rate in the general population. This central finding suggests there may be a predisposition for colorectal polyp formation in individuals with *CDH1* PLP variants.

Older age is a known risk factor for the development of colorectal adenomas. Colorectal adenomatous polyps may develop in up to 40% of individuals over the age of 60 and can be

found in up to 50% by the age of 70 years based on autopsy studies.[22] In our cohort, 46.9%

(15/32) of *CDH1* carriers over the age of 60 had at least one adenomatous polyp, a slightly

increased prevalence as compared to the general population. Recently, recommendations were

revised to advise that individuals at average risk for colorectal cancer should initiate cancer

screening at age 45 based on the observations that approximately 11% of colon cancers and 15%

of rectal cancers were diagnosed in individuals younger than 50 years.[23] In our study cohort we

found that over half of all patients younger than age 45 had at least one colorectal polyp, and half

of those individuals harbored at least one precancerous polyp. We found no difference in

prevalence of precancerous polyps in those younger than 45 when compared to older individuals.

Although the prevalence of colorectal polyps in younger individuals at average-risk is not well-

described, one study found approximately one third of patients under age 40 harbored

precancerous colorectal polyps.[24] Although our findings raise the possibility that germline *CDH1*

alterations may result in adenomatous polyps at a younger age, general population colon cancer

trends indicate that other factors could account for the findings in our study. Even though we

were unable to assess the rate of transformation of adenomatous lesions in this study, the low

prevalence of colorectal cancer in our *CDH1* cohort suggests the rate of malignant

transformation is the same as the general population. Nevertheless, our finding that a substantial

proportion of *CDH1* variant carriers younger than age 50 had preneoplastic colorectal polyps is

intriguing and could point to a role for early colorectal screening in this population.

Previous studies have suggested that some *CDH1* variants may increase the risk of

colorectal carcinoma. Specifically, a study by Lo et al. reported that families harboring *CDH1*

variants in the PRE-PRO region were more likely to be diagnosed with colorectal cancer.[19] Our

analysis revealed certain *CDH1* variants were associated with the presence of colorectal polyps,

which raises the possibility of a genotype-phenotype correlation. Another investigation of individuals with *CDH1* variants identified an association between missense variants affecting the extracellular regions of the E-cadherin protein and the presence of colorectal cancer.[25] Although we were unable to identify an association between *CDH1* variant type and a family history of colorectal cancer, our results warrant further observation of families with splice site and nonsense variants to determine if colorectal cancer is more prevalent compared to other *CDH1* variant types. An unexpected finding in the current study was the finding that a family history of breast cancer in a first-degree relative was an independent, negative predictor of the presence of colorectal polyps. This potentially protective effect of family history of breast cancer on colorectal polyp risk has not been described previously in this population. A potential explanation is a yet undefined genotype-phenotype correlation that would require a much larger cohort study. The most common location for adenomatous polyps and colorectal cancers is the proximal (right-sided) colon.[26, 27] Interestingly, in the current study of patients with germline *CDH1* variants we found the majority of colorectal polyps were located in the distal (left-sided) colon, and nearly half of all polyps were discovered in the sigmoid colon or rectum. Age greater than 60 years, female sex, and family history of colorectal cancer are risk factors for proximal (right-sided) colon lesions.[28] Unlike the general population, our analysis revealed no associations between the proximal colon lesions and older age, female sex, or family history of colorectal cancer. Even though our cohort size was limited, our findings could help identify factors among *CDH1* variant carriers that contribute to an increased likelihood of colorectal polyps. Given that most colorectal polyps were located in the distal colon there may be a role for flexible sigmoidoscopy, which could result in a safer, well-tolerated, and more efficient method of screening in this patient population.

There are important limitations to the current study worth noting. Notably, any data related to *CDH1* variant type, patient demographics, and personal and family cancer histories are subject to ascertainment bias. Furthermore, referral bias to our hereditary gastric cancer study may limit the applicability of our findings to other *CDH1* cohorts. In addition, colonoscopies in many younger patients in this study were frequently performed for diagnostic rather than cancer screening purposes. Many of the colonoscopies in this study were performed at other institutions, which potentially confounds the results. Rather than selecting a matched control population we elected to use previously published, population-based data for comparison of frequency of colonoscopy findings. Additionally, adenoma size, histopathology, and presence of high-grade dysplasia are associated with high risk for malignant transformation. However, we were unable to include these variables in the current analysis.

CONCLUSION

We observed a higher-than-expected prevalence of colorectal polyps especially among younger germline *CDH1* variant carriers undergoing colonoscopy. Additionally, we observed an association between splice site and nonsense gene variants and the detection of colorectal polyps. These data are relevant for cancer risk assessment and counseling of patients with *CDH1* PLP variants. Larger, multi-national cohort studies will be needed to study the possible associations between germline *CDH1* variants and colorectal cancer risk. In the meantime, our data suggest a potential role for targeted colorectal cancer surveillance in certain families with HDGC based on *CDH1* genotype and colorectal cancer history, potentially using flexible sigmoidoscopy given the higher prevalence of left sided colorectal lesions. Clinical and basic science research of

genotype-phenotype associations are needed to improve personalized cancer risk assessment and

clinical decision-making in patients with *CDH1* variants.

FIGURE AND TABLE LEGENDS

Figure 1. Study flow diagram and allocation of groups based on colon polyp detection for analysis.

Figure 2. Number of colon polyps found on colonoscopy per procedure.

Figure 3. Location of colon polyps among patients undergoing colonoscopy.

Figure 4. Number and type of colon polyps according to patient age.

Figure 5. Precancerous and benign colon polyps according to mutation type. *Includes all histologic colon polyp types (preneoplastic and benign)

Figure 6. Number and type of colon polyps according to patient age, by decade.

Figure 7. Association of Mutation Type/Domain with (a) Increased risk for presence of colon polyps; (b) Harboring multiple colon polyps and; (c) Presence of precancerous polyps.

Table 1. Patient demographics and clinical phenotypes according to presence or absence of colon polyps.

Table 2. CDH1 genotype according to presence and absence of colon polyps.

Supplemental Table 1A. Prevalence of *CDH1* PLP variant type and family histories of colorectal, gastric and lobular breast cancer

Supplemental Table 1B. Association between *CDH1* PLP variant type and family history of colorectal cancer

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Table 1. Patient demographics and clinical phenotypes according to presence or absence of colon polyps.

Variables	*CDH1* Cohort (N=85)	*CDH1* Patients with Colon Polyp (N=48)	*CDH1* Patients without Colon Polyps (N=37)	P-value
Age, years (mean $\pm$ SD)	53.8 ± 11.6	54.3 ± 11.6	53.1 ± 11.7	0.44
Sex				0.82
Females, N (%)	54 (61.4%)	30 (62.5%)	24 (64.9%)	
Males, N (%)	31 (35.2%)	18 (37.5%)	13 (35.1%)	
Race				1.00
White, (N, %)	83 (97.7%)	46 (95.8%)	37 (100%)	
African American (N, %)	2 (2.3%)	2 (4.2%)	0 (0%)	
BMI, kg/m^2 (mean $\pm$ SD)	$28.5 + 6.1$	$29.2 + 6.1$	$27.5 + 6.1$	0.18
Personal History of CRC (N, %)	1 (1.2%)	1 (2.1%)	0 (0%)	1.00
Family History CRC (N, %)	30 (35.3%)	17 (35.4%)	13 (35.1%)	1.00
1st/2nd degree relative (N, %)	24 (28.2%)	15 (31.3%)	8 (21.6%)	0.46
Family History Gastric Cancer[1] (N, %)	68 (80%)	42 (87.5%)	27 (72.9%)	0.10
Personal History Breast Cancer[2] (N, %)	19 (22.4%)	10 (20.8%)	9 (24.3%)	0.80
Family History Breast Cancer (N, %)	62 (72.9%)	30 (62.5%)	32 (86.5%)	0.02
1st degree relative (N, %)	41 (48.2%)	20 (41.7%)	21 (56.8%)	0.19
Family History of Cleft lip/palate (N, %)	6 (7.1%)	4 (8.3%)	2 (5.4%)	0.69
Underwent PTG (N, %)	37 (43.5%)	24 (50%)	13 (35.1%)	0.17
SRC foci identified[3] (N, %)	35 (94.5%)	22 (91.7%)	13 (100%)	1.00

[1] Family history of gastric cancer in 1st, 2nd, or 3rd degree relative.
[2] includes all histologic subtypes of breast cancer.
[3] Presence of signet ring cell carcinoma on gastric explant
CRC, colorectal cancer
PTG, prophylactic total gastrectomy
SRC, signet ring cells

Table 2. *CDH1* genotype according to presence and absence of colon polyps.

Variables	*CDH1* Cohort (N=85)	*CDH1* Patients with Colon Polyps (N=48)	*CDH1* Patients without Colon Polyps (N=37)	P-value
Mutation Type				
Deletion	13 (15.3)	11 (22.9)	2 (5.4)	0.27
Frameshift	13 (15.3)	7 (14.6)	6 (16.2)	
Missense	14 (16.5)	7 (14.6)	7 (18.9)	
Nonsense	19 (22.4)	10 (20.8)	9 (24.3)	
Splice site (Canonical)	26 (30.6)	13 (27.1)	13 (35.1)	
Domain[1]				
Cadherin	38 (44.7)	20 (41.6)	18 (48.6)	0.97
Transmembrane	13 (15.3)	5 (10.4)	8 (21.6)	
Cytoplasmic	3 (0.04)	3 (6.2)	0 (0.0)	
PRO	10 (11.7)	5 (10.4)	5 (13.5)	
PRE	3 (0.04)	1 (2.1)	2 (5.4)	
Linker region	3 (0.04)	2 (4.2)	1 (2.7)	

[1]Domain data available for 70 patients
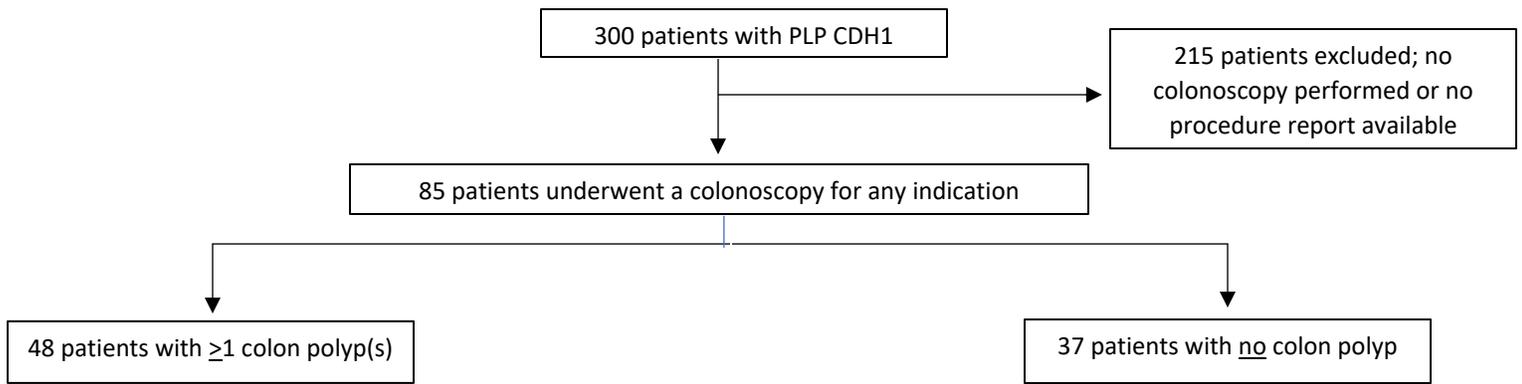
```
┌─────────────────────────────┐
│  300 patients with PLP CDH1 │
└─────────────────────────────┘
              │                          ┌──────────────────────────────┐
              │──────────────────────────▶  215 patients excluded; no    │
              │                          │  colonoscopy performed or no  │
              ▼                          │  procedure report available   │
┌───────────────────────────────────────┴──────┐
│ 85 patients underwent a colonoscopy for any   │
│                indication                     │
└───────────────────────────────────────────────┘
         │                                          │
         ▼                                          ▼
┌──────────────────────────────┐   ┌──────────────────────────────┐
│ 48 patients with >1 colon    │   │ 37 patients with no colon     │
│         polyp(s)             │   │          polyp                │
└──────────────────────────────┘   └──────────────────────────────┘
```

Figure 1. Study flow diagram and allocation of groups based on colon polyp detection for analysis.
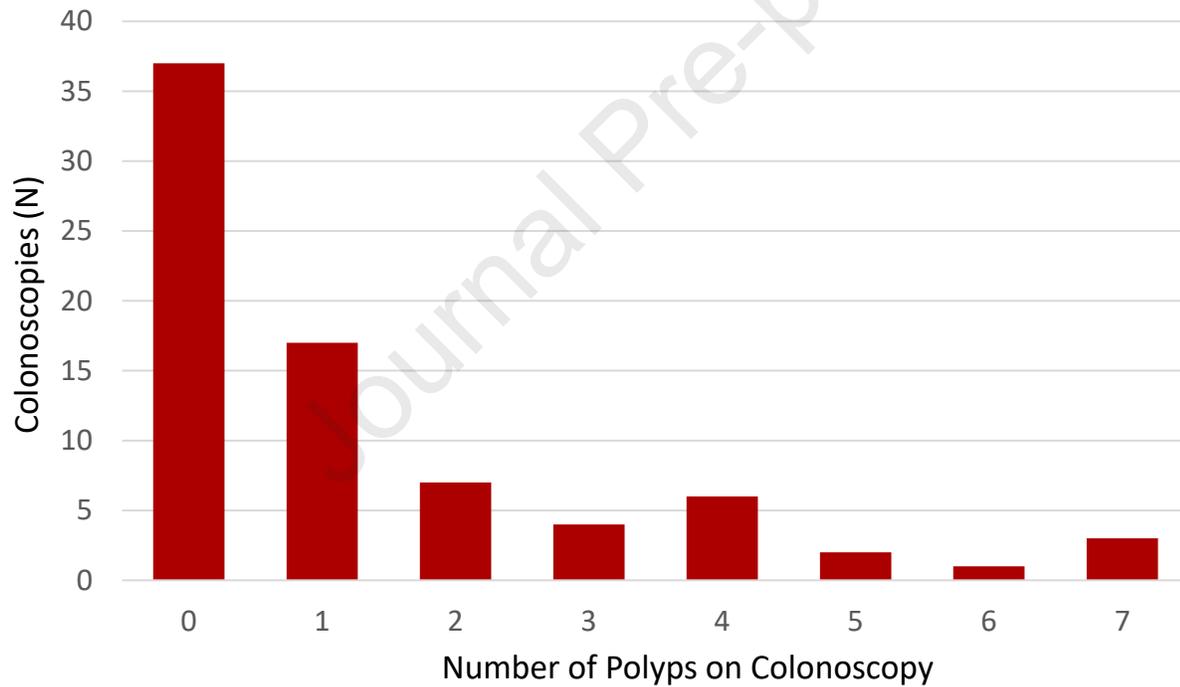
Figure 2. Number of colon polyps found on colonoscopy per procedure

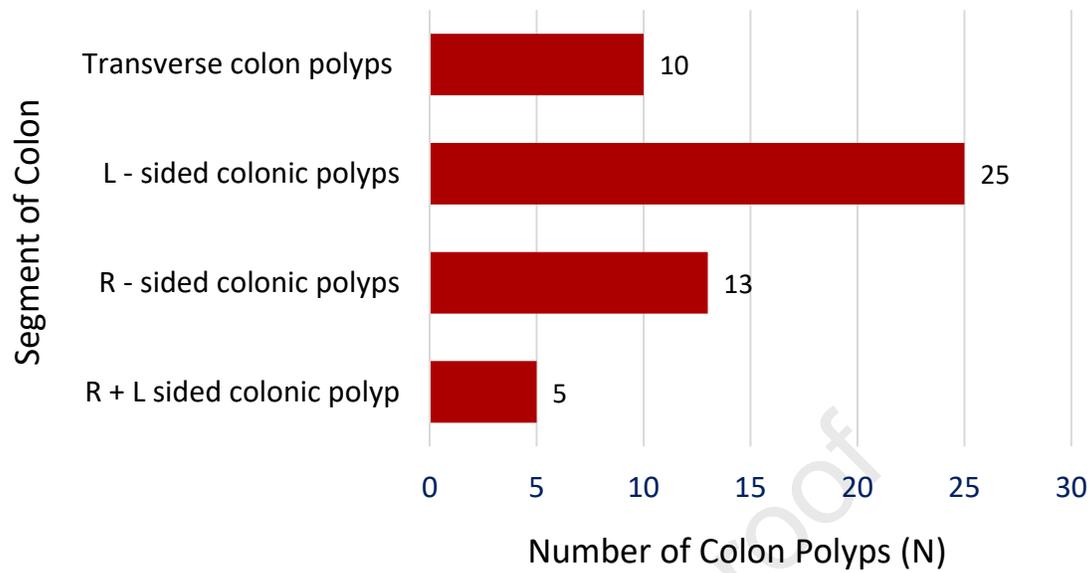*Includes all histologic polyp types (preneoplastic and benign)

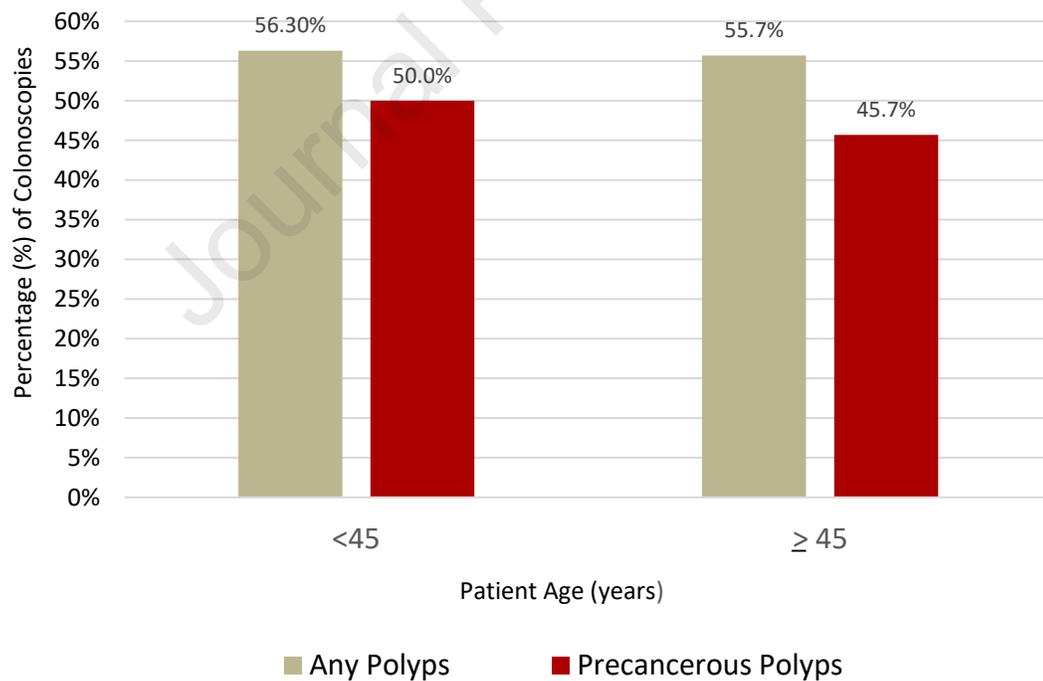**Figure 3.** Location of colon polyps among patients undergoing colonoscopy.

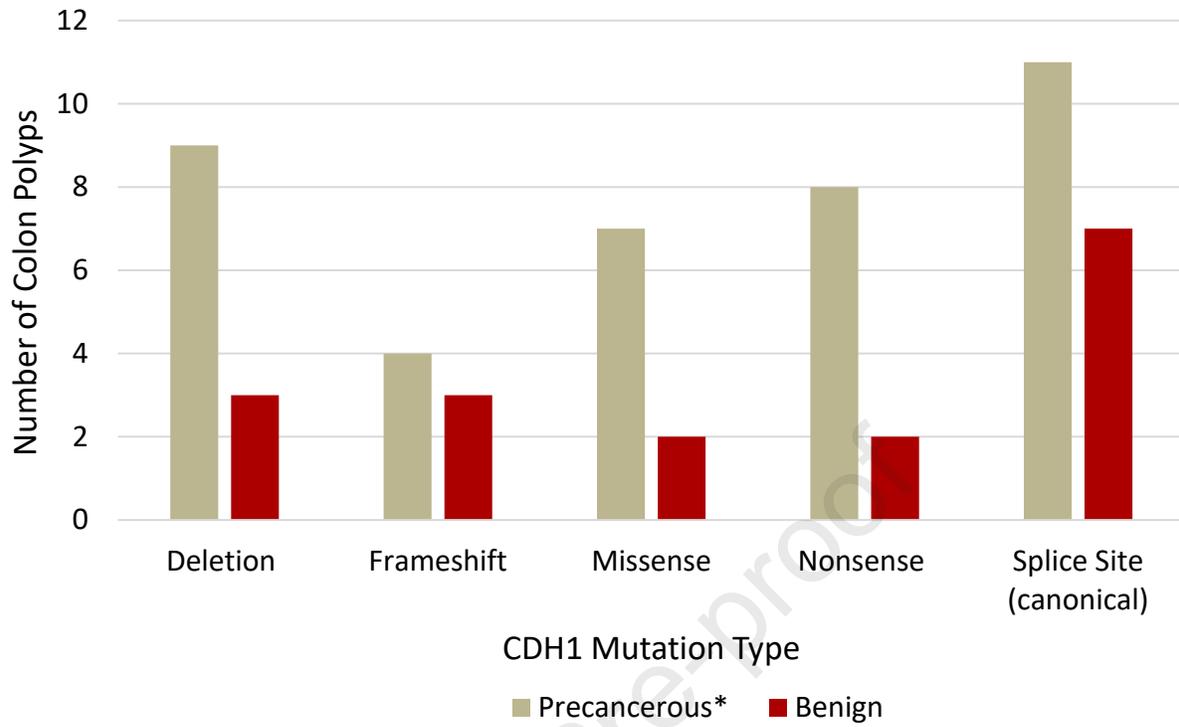**Figure 4.** Number and type of colon polyps according to patient age.

Figure 5. Precancerous and benign colon polyps according to mutation type.
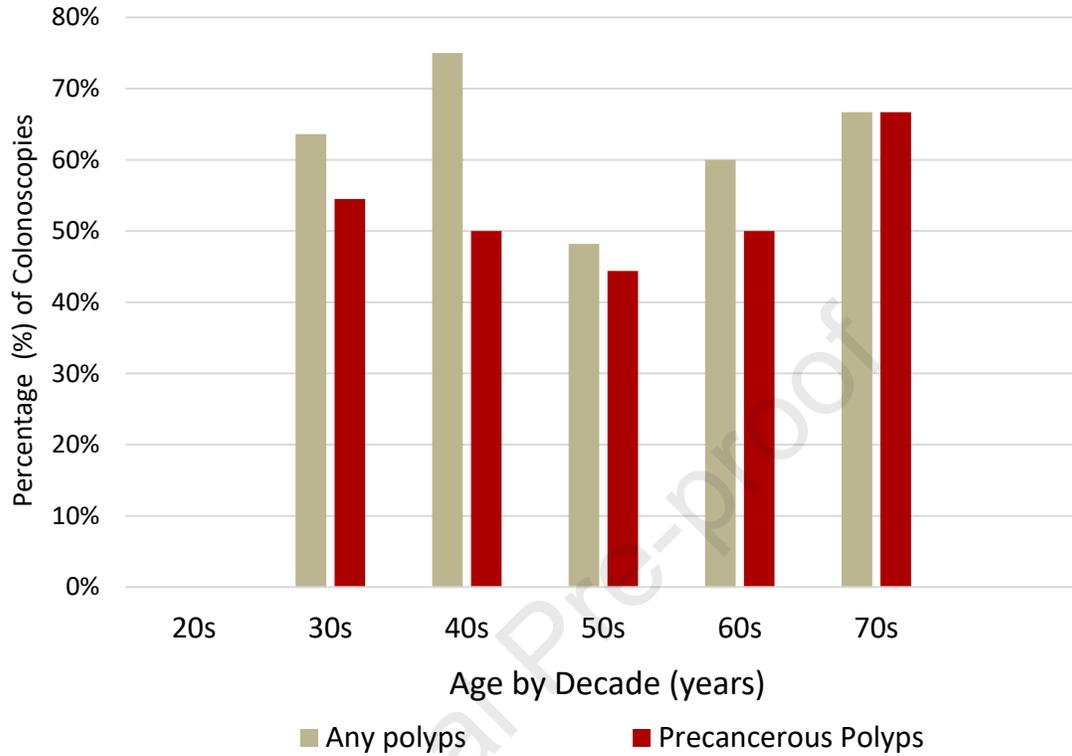
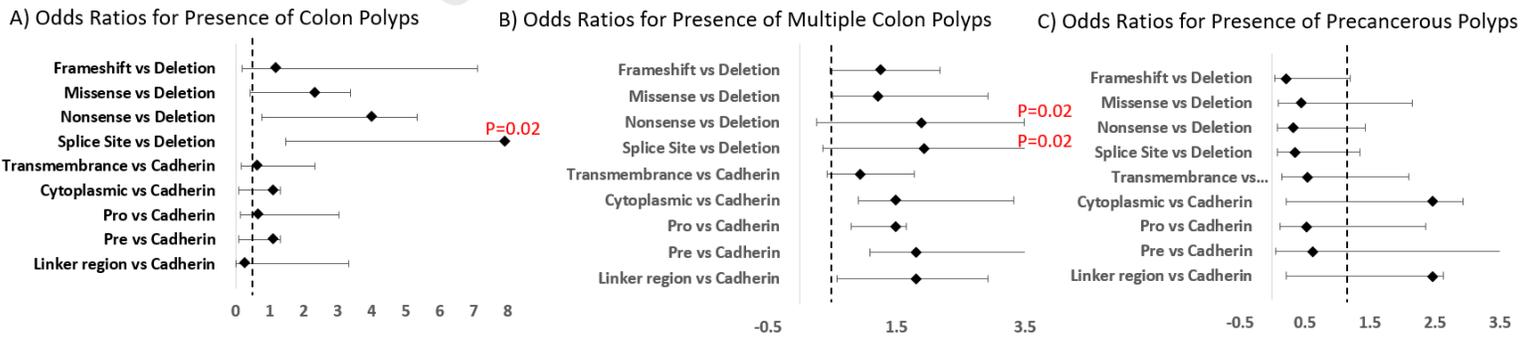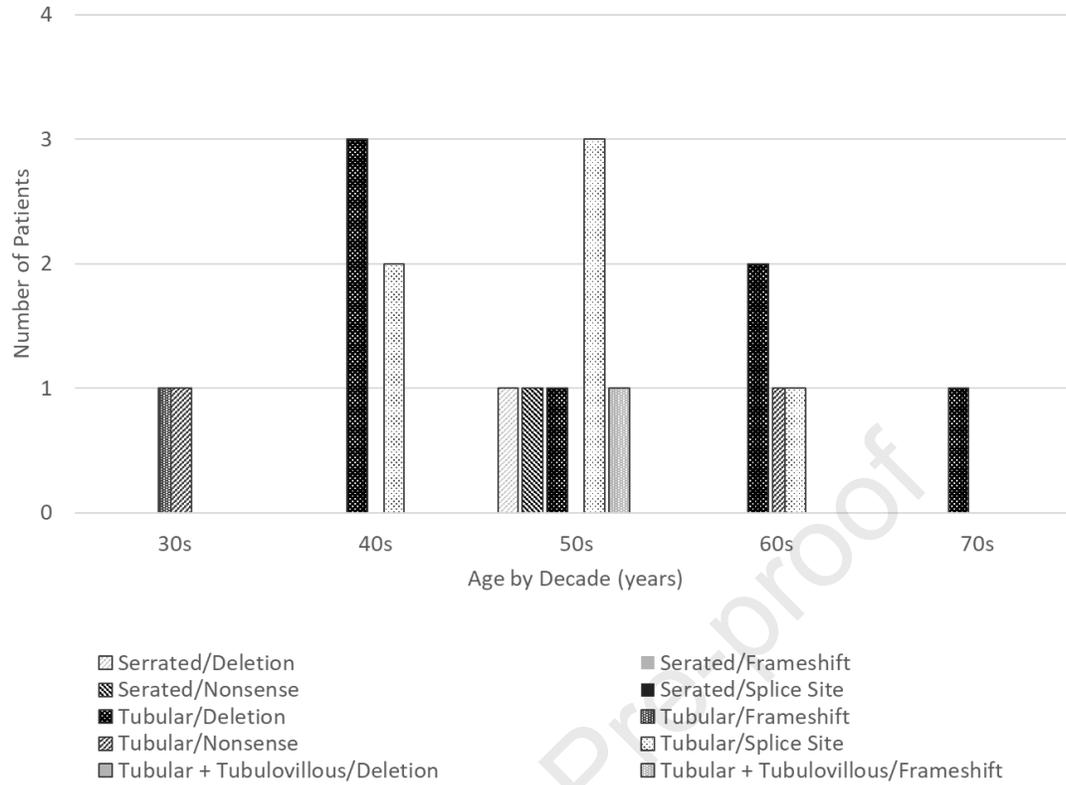**Figure 6.** Number and type of colon polyps according to patient age, by decade.

Figure 7. Association of Mutation Type/Domain with (a) Increased risk for presence of colon polyps; (b) Harboring multiple colon polyps and; (c) Presence of precancerous polyps.

Supplemental Figure 1. Histologic subtype of polyp and CDH1 variant by age (decade)