Analysis of missense variants in *RPS20* and an association with colorectal cancer predisposition

Author Information: Jennifer Herrera-Mullar,[1] Cassidy Carraway,[1] Ashley PL Marsh,[1] Zahra Heidari,[1] Rachel Jones,[1] Felicia Hernandez,[1] Emily Kudalkar,[1] Marcy E. Richardson[1]

1. Ambry Genetics Corporation

Presenting Author Information: Jennifer Herrera-Mullar, MGC, LCGC, DMA
jherreramullar@ambrygen.com

Keywords: colorectal cancer; hereditary cancer; multigene panel testing; familial colon cancer

Background and Aim
RPS20 has been posited as a colorectal cancer (CRC) predisposition gene, but only six families have been published in the literature. Four families harbor loss-of-function (LoF) variants, and two harbor missense variants with unknown impact. We studied 36 individuals with LoF variants showing 45-fold odds of CRC relative to a negative multigene panel testing (MGPT) cohort. (wildtype, WT; p=< .001), characterizing CRC risks similar to *MLH1*. However, data is lacking on the association of *RPS20* missense variants with CRC. Here, we assess the CRC prevalence in >500 individuals with *RPS20* missense variants.
Methods
Retrospective review of individuals undergoing pan-cancer MGPT (17-91 genes) between 01/2019-04/2024 revealed 513 individuals carrying 125 rare, heterozygous missense variants in *RPS20*. Variants were pooled by computational predictor to select the most likely deleterious variants. Using ICD-10 data, CRC prevalence was compared among *RPS20* missense and a WT MGPT cohort ascertained during the same period. Three variants were selected for structural assessment based on past literature and/or clinical history.
Results
Carriers of 125 unique missense variants in *RPS20* showed no significant enrichment of CRC relative to WT (OR 0.94 95% CI [0.6,1.5] p=.91). When stratifying based on computational predictors, variants with the most deleterious predictions showed the greatest prevalence of CRC, but this was not statistically significant (OR 1.85 95% CI [0.7,4.2] p=.15). Structural analyses of previously reported p.Glu33Val and p.Val54Leu variants did not predict significant destabilization, but a clinically suspicious variant (p.Leu24Pro) identified in our cohort is anticipated to moderately decrease structural stability.
Conclusions
Initial analyses of pooled *RPS20* missense variants did not show a statistical association with CRC; however, combined computational, structural, and clinical data may be utilized to identify rare pathogenic missense variants. Further study of predicted-damaging variants is warranted in larger cohorts, as ours may be underpowered to detect increased odds of CRC.

Table 1: Selected missense variants

Cohort	Ascertainment	Family	Patient	Genotype	BayesDel score (ACMG points)	Alpha-missense score (ACMG points)	SpliceAI	Structural analysis	Sex	Phenotype (age at diagnosis)
Broderick, et al. 2017 PMID: 27713038	Cohort of individuals with CRC meeting Amsterdam I/II criteria	1	1	c.160G>C p.Val54Leu	0.20 (+1)	0.9587 (+2)	<0.1	Inconclusive; stabilizing (-0.5244 kcal/mol)	M	Colon (41)
Djursby, et al. 2020 PMID: 33193653	Families meeting Amsterdam I/II criteria	2	2	c.98A>T p.Glu33Val	0.43 (+3)	0.9987 (+4)	DL 0.03, DG 0.77	Inconclusive; negligibly destabilizing (0.789 kcal/mol)	F	Colon (67, 73)
			3						F	Cecum (37), rectum (73)
			4						F	Colon (60)

			5						F	Vulva (47)
			6						M	Colon (59)
			7						F	Colon (24)
This cohort	Individuals undergoing MGPT for diverse cancer indications	3	8	c.71T>C p.Leu24Pro	0.49 (+3)	0.9997 (+4)	<0.1	Conclusive; moderately destabilizing (6.033 kcal/mol)	F	Colon (26), breast (44)
		4	9						F	Rectal (51)