Characterization of *RPS20*-related colorectal cancer predisposition: a case series from a multigene panel testing cohort

Jennifer Herrera-Mullar, Ashley PL Marsh, Cassidy Carraway, Felicia Hernandez, Emily Kudalkar, Marcy Richardson

BACKGROUND

- Current established genes associated with early-onset hereditary colorectal cancer (CRC) explain less than 20% of hereditary CRC.
- *RPS20* was first implicated as a candidate gene for hereditary CRC in 2014, but only 5 families have been published in the literature.
- The Clinical Genome Consortium considers the *RPS20*-related CRC gene-disease relationship (GDR) as Limited, meaning no variants can be classified as likely pathogenic of pathogenic (LP/P).
- *RPS20* is not currently included in ASCO guidelines for hereditary cancer testing and is listed in the NCCN guidelines as having only limited evidence for CRC predisposition.

METHODS

Retrospective review of ~950,000 multigene panel testing (MGPT) orders for diverse cancer indications

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Individuals with putative loss-of-function variants (pLOF) in *RPS20* underwent comprehensive phenotype curation

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ICD10 codes used for comparative analysis of CRC prevalence in *RPS20* cohort (n=36) and a Lynch syndrome cohort (n=11,437) versus a wildtype (WT) cohort (MGPT-negative, 36-85 genes; n=384,445) using Fisher's exact test

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Age at diagnosis plotted for *RPS20* and Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6* and *PMS2)* using Kaplan-Meier

FIGURE 1A. Phenotypes in 36 individuals heterozygous for pLOF in *RPS20*

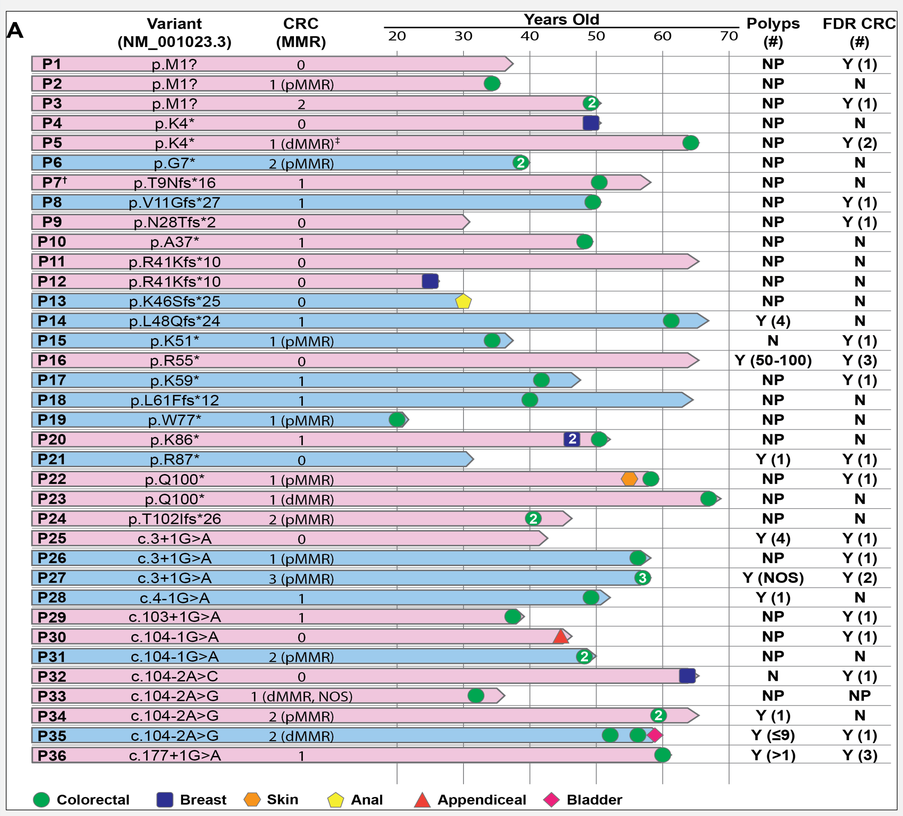


FIGURE 1B. Forest plot comparing prevalence of CRC in individuals with pLOF in *RPS20* and LP/P in Lynch syndrome genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) compared to a similarly ascertained WT MGPT cohort

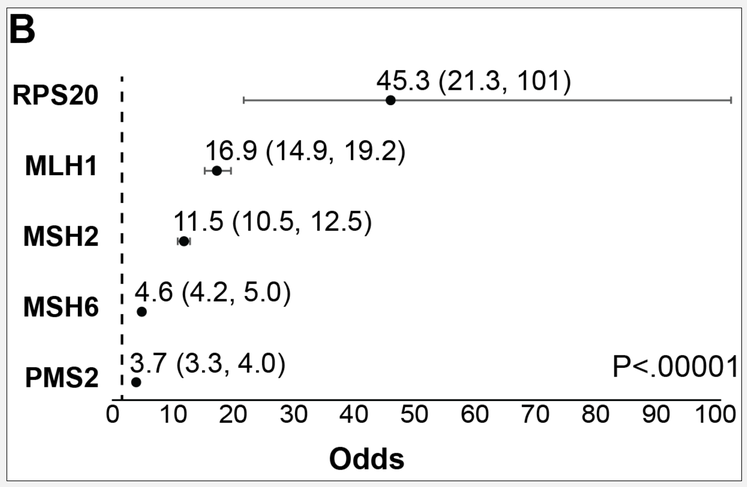
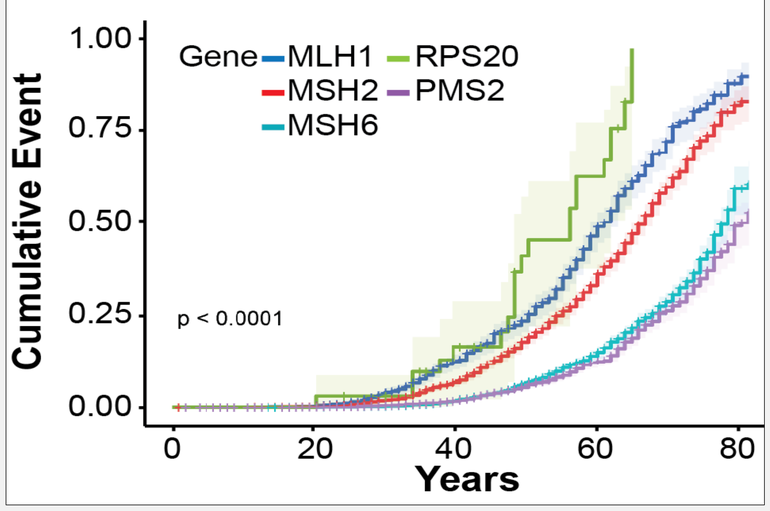


FIGURE 1C. Kaplan-Meier plot showing comparison of age of diagnosis among *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *RPS20* cohorts



RESULTS

- 28 unique *RPS20* pLOF detected in 36 individuals (overall cohort frequency of 0.004%)
- Median age of CRC diagnosis in *RPS20* cohort was 48.25 years
- 16.7% (6/36) individuals reported multiple primary CRC diagnoses
- Majority of CRC tumors pMMR (71.4%; 10/14)
- Signet ring cell CRC in 11.1% (4/36)
- CRC more prevalent in *RPS20* cohort than the *MLH1* cohort (OR 45.3 versus OR 16.9) compared to WT

TAKE HOME POINTS

- Comparison of CRC prevalence showed a statistically significant two-fold enrichment compared to an *MLH1*-related Lynch syndrome (LS) cohort.
- These data elevate the GDR score from Limited to Moderate for *RPS20*-related CRC predisposition, allowing for classification of variants as LP/P.
- Management of CRC risk in *RPS20* heterozygotes may mirror *MLH*1-related LS, with attention given to the potential risk of multiple primary CRCs.

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