Title: Beyond the usual suspects: features of hereditary colorectal cancer in a *CHEK2* cohort

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Background: Genetic testing for individuals with a personal and/or family history (hx) suggestive of a hereditary colorectal cancer (HCC) syndrome may not identify a causative mutation in genes associated with well-known HCC syndromes such as Lynch Syndrome (LS), Familial Adenomatous Polyposis (FAP), Attenuated FAP (AFAP) or *MUTYH*-Associated Polyposis (MAP) suggesting other genetic causes of HCC may be appropriate for investigation. Multiple studies indicate pathogenic mutations in *CHEK2* increase the risk of developing various cancers including colon, breast, and others. The purpose of this study was to describe the features of well-characterized HCC syndromes in a *CHEK2* cohort to assess appropriateness for *CHEK2* testing in this population. **Methods**: Clinical histories of 594 patients who underwent multi-gene panel testing for a broad spectrum of hereditary cancers between 3/2012-12/2014 and harbored a pathogenic/likely pathogenic *CHEK2* mutation were queried. Multiple mutation carriers were excluded from analysis (n=59). The cohort was analyzed for features of LS and FAP/AFAP/MAP per National Comprehensive Cancer Network (NCCN) guidelines v1.2015. **Results**: Clinical histories were available for 535 *CHEK2* mutation carriers. **[LS]** Of those with a personal hx of cancer (n=461), 10.2% (47/461) reported hx of colorectal cancer (CRC; average age of diagnosis: 48 years), and 23.6% (109/461) reported at least one LS tumor as defined by NCCN. Of those who had LS tumors, 9.2% (10/109) had multiple LS tumors: all met revised Bethesda criteria (BC) and none met Amsterdam II criteria (ACII). Of those in the *CHEK2*-positive cohort who provided personal and family hx information (n=524), 7.8% (41/524) met BC and 2.1% (11/524) met ACII. 41.5% (17/41) meeting BC harbored the 1100delC mutation compared to 81.8% (9/11) of those meeting ACII. Of those who met both ACII and BC (<1%, 3/524), all harbored the 1100delC mutation. Immunohistochemistry results were reported for 3.6% (19/524) individuals and were abnormal for 15.7% (3/19), all harboring non-1100delC mutations. **[FAP/AFAP/MAP]** 17.5% (94/535) of *CHEK2*-positive individuals reported a personal hx of colon polyps (CP), none reporting greater than 100 CP. 57.5% (54/94) reported adenomatous CP. 59.3% (32/54) reported having $\leq$ 5 CP, and 59.3% (32/54) harbored non-1100delC mutations. No individuals met criteria for FAP whereas 22.2% (12/54) met testing criteria for AFAP/MAP. 42.5% (40/94) reported non-adenomatous CP. 62.5% (25/40) reported having $\leq$ 5 CP, and 67.5% (27/40) harbored non-1100delC mutations. Other reported CP types included hyperplastic, inflammatory, juvenile and hamartomatous. **Conclusions**: In this cohort of *CHEK2*-positive patients ascertained via multi-gene panel testing, a portion of patients exhibited clinical features of well-known HCC syndromes, particularly LS and AFAP/MAP, suggesting that *CHEK2* may contribute to a subset of HCC. The identification of both 1100delC and non-1100delC alterations indicates that *CHEK2* testing in the HCC setting should be comprehensive rather than targeted. Further studies comparing the frequency of *CHEK2* mutations between HCC cohorts and the general population as well as comparing phenotypes between *CHEK2* positive cohorts and LS/*APC*-positive cohorts are needed to further define the contribution of *CHEK2* to HCC.