Search for Novel Predisposing Gene Variants and Cancer Predictive Markers in Hereditary Colon Cancer Syndromes

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ABSTRACT

Abbreviations: CRC: Colorectal Cancer; HNPCC: Hereditary Non-Polyposis Colorectal Cancer; FAP: Familial Adenomatous Polyposis; MAP: MUTYH-Associated Polyposis; NGS: Next Generation Sequencing

Opinion

The introduction of Next Generation Sequencing (NGS) technology in clinical practice has had a profound impact in the identification of gene variants responsible for heritable diseases. The high throughput capability of NGS allows the simultaneous screening of the whole coding genome (usually defined clinical exome) at affordable costs and with reasonable turnaround times. While the traditional single gene sequencing approach had low detection power, NGS greatly expanded the number of tested genes in many genetic conditions where disease predisposition can be due to causative mutations in many different genetic loci. In Colorectal Cancer (CRC), which account for 10% of all newly diagnosed cancers and is responsible for 9% of all cancer deaths, family history is a major risk factor [1-3]. It is estimated that approximately a quarter of all CRCs is due to familial inheritance with 5-8% of cases attributable to single gene inherited predisposition [4,5]. Traditionally, three major types of inherited predisposition to CRC are recognized being the Lynch syndrome (previously known as Hereditary Non-Polyposis Colorectal Cancer or HNPCC), Familial Adenomatous Polyposis (FAP), and the MUTYH-Associated Polyposis (MAP).

These three CRC-predisposing conditions are mainly caused by pathogenic variants in six primary genes (MLH1, MSH2, MSH6, PMS2, APC, and MUTYH). However, several additional genes are also known to cause hereditary CRCs or conferring an increased risk for colorectal cancer. Thanks to NGS technology, the labor extensive and time-consuming Sanger sequencing approach has been replaced by multigene panels that allow for an inexpensive and comprehensive screening for numerous hereditary CRC genes. Yet, NGS has been less successful in identifying novel CRC-predisposing genes [6,7]. Indeed, a PubMed search (accessed on February 5th 2020) using the terms “new colorectal cancer gene” and “novel colorectal cancer gene” , reveals that documents retrieved were constantly increasing in the five years period 2010-2014, while remained steady in the following 2015-2019 period (Figure 1). The National Cancer Comprehensive Network (NCCN), has recently recommended a list of 22 genes to be included in multigene testing panel for hereditary CRCs [8]. However, for all the 22 genes, the missense variants listed at Varsome (accessed 30th January 2020), and classified as of unknown significance (VOUS), largely outnumber variants classified as pathogenic or likely pathogenic (Table 1).
Table 1: Missense variants of unknown significance in NCCN CRCs genes included in multigene panels.

| Gene   | Gen Bank accession number | Number of missense variants classified as VOUS | Total number of missense variants | Missense VOUS/Total ratio (%) |
|--------|---------------------------|-----------------------------------------------|-----------------------------------|-------------------------------|
| APC    | NM_000038.6               | 2691                                          | 2781                              | 96.8                          |
| ATM    | NM_000051.3               | 3320                                          | 3556                              | 93.4                          |
| AXIN2  | NM_004655.4               | 599                                           | 619                                | 96.8                          |
| BLM    | NM_000057.4               | 511                                           | 547                                | 93.4                          |
| BMPR1A | NM_004329.2               | 383                                           | 409                                | 93.6                          |
| CHEK2  | NM_00105735.2             | 859                                           | 905                                | 94.9                          |
| EPCAM  | NM_002354.3               | 68                                            | 82                                 | 82.9                          |
| GALNT2 | NM_004481.5               | 2                                             | 5                                  | 40                            |
| GREM1  | NM_013732.7               | 5                                             | 6                                  | 83.3                          |
| MLH1   | NM_000249.3               | 797                                           | 1059                               | 75.2                          |
| MLH3   | NM_001040108.1            | 137                                           | 200                                | 68.5                          |
| MSH2   | NM_000251.3               | 1356                                          | 1521                               | 87.8                          |
| MSH6   | NM_000179.2               | 1948                                          | 2058                               | 94.6                          |
| MUTYH  | NM_001182425.1            | 564                                           | 646                                | 87.3                          |
| NTHL1  | NM_002528.7               | 147                                           | 159                                | 92.4                          |
| PMS2   | NM_000535.7               | 1031                                          | 1117                               | 92.3                          |
| POLD1  | NM_001256849.1            | 787                                           | 832                                | 94.6                          |
| POLE   | NM_006231.4               | 1518                                          | 1601                               | 94.8                          |
| PTEN   | NM_000314.8               | 128                                           | 303                                | 42.2                          |
| SMAD4  | NM_005359.6               | 281                                           | 301                                | 80                            |
| STK11  | NM_000455.5               | 449                                           | 500                                | 89.8                          |
| TP53   | NM_001276760.2            | 1151                                          | 1635                               | 70.4                          |

Thus, it is possible that the missing heritability of familial colorectal cancer could be explained by a re-evaluation of the putative pathogenic role of VOUS, at least in some families, rather than attributable to yet unknown predisposing genes. Recent work has demonstrated the utility of machine learning training in decreasing the number of VOUS in different disease-causing genes [9,10]. Similar approaches could be useful also applied to hereditary cancer syndromes. Another unresolved issue in hereditary predisposition to CRCs is the lack of sensitive and reliable blood-based tests to diagnose cancer in its early preclinical stages that would be pivotal in reducing the cancer burden in patients at high risk. Though, like the search for novel CRC predisposing genes, the number of PubMed documents retrieved using the search term “blood-based colorectal cancer detection” raised constantly in the 2010-2014 period while plateauing in the following five years (2015-2019, Figure 2). Despite the huge emphasis that the concept of “liquid biopsy” has provoked in cancer screening as an attractive tool for early detection and minimally invasive diagnosis of cancer, the sensitivity and the specificity achieved so far prevented these tests to be used in general population screening (reviewed in [11-15]).

The liquid biopsy approach has been focused on analyzing either Circulating Tumor Cells (CTCs), cell-free circulating tumor DNA (cfDNA) and/or tumor-derived extracellular vesicles (exosomes).
Liquid biopsy approaches have been proven extremely useful in monitoring cancer recurrence, progression, efficacy of therapeutic intervention as well as disease profiling, considering the clonal heterogeneity of human cancers [16,17]. Blood-based screening methods were less effective in detection of cancer in early preclinical stages. However, a recent study demonstrated that using a machine learning approach it is possible to achieve high sensitivity and specificity applying whole-genome sequencing of cell-free DNA on a cohort of predominantly early stage CRCs [18]. In this light, tumors exhibiting Microsatellite Instability (MSI), may represent a promising target for future applications. In fact, several recent works have determined that the MSI phenotype may be detected directly from cell-free DNA [19-23]. In conclusion, recent advances should help in a more effective monitoring of patients with high CRC risk and the long-term surveillance of their health status.

Declaration of Conflict Interest

The author declares no potential conflict of interest with respect to the research, authorship, and/or publications of this article.

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