Multi-gene hereditary cancer panel testing identifies novel GREM1 duplication and BRCA1 mutation in patient with multiple colon polyps

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Introduction
Recent studies have identified mutations in the 5’ regulatory region of GREM1 as causal in families of Ashkenazi Jewish descent with Hereditary Mixed Polyposis Syndrome (HMPS), and in a family with Attenuated Familial Adenomatous Polyposis (AFAP). The GREM1 gene product is a transcription enhancer, and duplications in it are associated with Hereditary Mixed Polyposis Syndrome (HMPS), an autosomal dominant inherited syndrome characterized by multiple types of colorectal polyps1-3. Individuals with HMPS have increased risk for colorectal cancer, but do not appear to develop extra-colonic cancers or other clinical features4.

The following GREM1 duplications have been reported in the literature:
• 40 kb duplication (Chr15:g.32964393_33004759) identified in HMPS families of Ashkenazi Jewish descent
• 16 kb duplication (Chr15:g.32986220_33002449) identified in a Swedish family with attenuated/atypical polyposis
• 57 kb duplication encompassing the entirety of the GREM1 gene, its upstream regulatory region, and part of the neighboring gene SCGS in a patient diagnosed with sigmoid colon carcinoma at the age of 355.

Here, we present a case study that suggests testing for GREM1 mutations may be appropriate for individuals with polyposis or a clinical suspicion of Lynch syndrome independent of ethnicity.

Methods
This individual received genetic testing from Color Genomics using an NGS-based 30-gene panel for hereditary cancer risk, including the following genes: APC, ATM, BAP1, BARD1, BMPRIA, BRCA1, BRCA2, BRIPI, CDH1, CDK4, CDKN2A, CDKN2B, CHEK2, EPCAM, GREM1, MTF1, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, POLQ, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53. Copy number changes were assessed based on read depth analysis. A dedicated split read detection algorithm was used to identify structural variants. Subsequent Sanger sequencing was used to confirm the presence of detected variants.

Discussion
• This case highlights the clinical utility of broader panel testing, even in a patient who presented with a history consistent with a classic cancer syndrome.
• Limited Lynch syndrome-related testing in this patient would have led to an uninformative negative result, missing both the BRCA1 and GREM1 mutations.
• This finding supports testing for mutations in the regulatory region of the GREM1 gene in individuals of all ethnicities with a history of multiple colorectal polyps.
• GREM1 duplications should also be considered in the differential diagnosis of Lynch syndrome due to some phenotypic overlap.

Case Study
• A novel GREM1 duplication and a BRCA1 mutation were identified in a 63-year old Caucasian non-Ashkenazi Jewish female.
• She had been followed for years as if she had Lynch syndrome due to her strong family history fulfilling Amsterdam Criteria.
• This patient has an especially strong cancer history on her maternal side, where 3 of 5 siblings had reported colon cancer. Colon cancer was also observed in one paternal aunt. Lineage of these mutations has not yet been established, and is complicated by the fact that her parents are first cousins. In addition, her brother has a reported history of polyps, but the polyp status for any other relatives is unknown.
• Since the age of 46, she had colonoscopies every 3-5 years which revealed over 15 colon polyps, including 8 tubular adenomas and 2 hyperplastic polyps (pathology not available for all).

• Based on the high clinical suspicion of Lynch syndrome, she had a total hysterectomy and oophorectomy at age 62.
• She was initially recommended to take a 19-gene panel test for hereditary breast and ovarian cancer risk that included Lynch syndrome-associated genes. However, even in a patient who presented with a history consistent with a classic cancer syndrome.
• Therefore, she was referred for broader testing via a 30-gene panel with additional colorectal cancer genes. The 30-gene test revealed a novel 23.9kb tandem duplication involving the 5’ regulatory region of GREM1 (Chr15:g.32987207_33011059). This duplication partially overlaps with the previously published duplications.

References