A retrospective analysis of discrepancies between genotypes and phenotypes on next generation sequencing colon cancer panels (ColoNext NGS): Implications for clinical diagnosis

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Abstract:

The launch of Ambry's cancer NGS panels in early 2012 has led to unexpected genotype-phenotype discrepancies among patient results. We reviewed 38 ColoNext NGS cancer panels that had mutations detected in genes associated with cancer syndromes with established clinical criteria. Of those, a significant percentage of patients with pathogenic mutations did not meet the correlating clinical criteria based on their personal and family history: 50% (3/6) with biallelic MUTYH mutations, 50% (2/4) with SMAD4 mutations, 50% (1/2) with PTEN mutations, 14% (1/7) with APC mutations, 40% (2/5) with MSH6 mutations, 28.5% (2/7) with MSH2 mutations, and 57% (4/7) with PMS2 mutations. Here we discuss specifics in twelve of these cases. Biallelic MUTYH gene mutations were detected in three unrelated individuals with early onset colon cancer and less than 20 adenomatous colon polyps. A SMAD4 mutation was detected in a proband with gastric cancer at age 35 who was later found to have 20-99 colon/GI polyps of varying pathology types, none of which were juvenile, by age 50. Another SMAD4 mutation was found in a proband diagnosed with colon cancer at age 30 with normal tumor MSI and IHC testing. A PTEN mutation was identified in a 65 year old individual with over 100 adenomatous colon polyps and no family history of cancer. An individual with 2-5 adenomatous polyps and colon cancer at age 39 was found to carry an APC mutation. A 16 year old with colon cancer and a reported heavy polyp load was found to carry two MSH6 mutations. A 36 year old unaffected individual with a MSH2 mutation was tested due to a paternal family history of sarcoma, endometrial, and late onset colon cancers. An intronic MSH2 mutation was found in a patient with endometrial cancer at age 48 but whose family history was not suggestive of Lynch Syndrome. A single exon PMS2 deletion was found in a proband with 2-5 colon polyps, colon cancer at age 49, and normal MSI and IHC tumor testing. A proband meeting Cowden syndrome clinical criteria was found to carry a PMS2 mutation. Since these results reveal that genotype-phenotype discrepancies clearly exist among individuals carrying mutations in well-known cancer syndrome genes, we propose continued evaluation of the clinical features associated with each condition. We encourage the continued reporting of additional cases with uncharacteristic correlations in order to further expand upon the clinical criteria utilized in current diagnostic processes.