New cancer type with PIK3CA mutations

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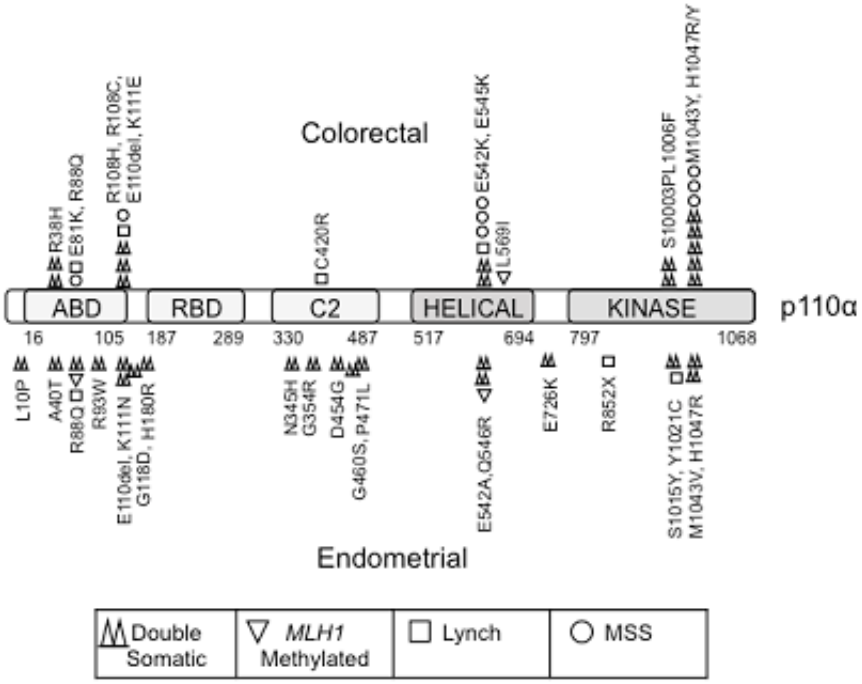

Localization of PIK3CA mutations (relative to functional domains of encoded protein p110α) in colorectal and endometrial cancer by MSI type. Credit: Drs. Stacey Cohen and Colin Pritchard

A newly defined type of colorectal and endometrial cancer involves at least two somatic mutations in the mismatch repair genes (MMR): MLH1, MSH2, MSH6, PMS2. This double somatic MMR cancer has no germline mutations in the MMR genes, unlike tumors due to hereditary

Lynch syndrome. Double somatic MMR cases, along with Lynch syndrome and MLH1 gene hypermethylation cases, exhibit microsatellite instability (MSI). This hypermutable phenotype is caused by the loss of DNA mismatch repair activity.

There is a need to improve our understanding of the molecular features distinguishing these three MSI subgroups. Doing so can better inform future cancer risk and can potentially lead to new therapies.

Drs. Stacey Cohen (Clinical Research Division), Colin Pritchard (Department of Lab Medicine), and colleagues sought out to accomplish this. The investigators compared the molecular features of double somatic MMR, Lynch syndrome, MLH1 hypermethylated, and microsatellite stable (MSS) colorectal and endometrial cancers. Specifically, they examined the mutation prevalence among these cancer subgroups, focusing on mutations in five key genes in the epidermal growth factor receptor (EGFR) and phosphoinositide-3-kinase (PI3K) pathway: KRAS, NRAS, BRAF, PIK3CA, and PTEN. The results from their study were recently published in *Gastroenterology*.

Using two prospective studies, Hereditary Nonpolyposis Colorectal Cancer Study and the Ohio Colorectal Cancer Prevention Initiative, the investigators identified double somatic MMR patients as those with colorectal and endometrial tumors who had two or greater somatic (but not germline) mutations in MMR genes. Using targeted next-generation sequencing, they found among colorectal cancer cases that that 14/21 (67%) of patients with double somatic tumors also had PIK3CA mutations, compared to 4/18 (22%) of tumors from patients with Lynch syndrome, 2/10 (20%) tumors with MLH1 hypermethylation, and 12/78 (15%) tumors with microsatellite stability (Fisher's exact test, P