“Genomewide Discovery of Novel Cancer Predisposing Mutations”

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Abstract: Identifying cancer predisposing mutations can provide new biological insights and significantly impact important clinical decision making regarding treatment, surveillance and preventive approaches. Examples include the BRCA1 breast cancer susceptibility gene, which affects treatment decisions (surgical management), surveillance (frequent breast MRI) and prevention (oophorectomy for prevention of ovarian cancer). Hereditary breast, colon, hematologic and multiple primary cancer patients commonly present to Cancer Genetics clinics, but the majority of these patients do not have identifiable mutations in known candidate genes. Here, we will combine three unique ascertainment of cancer-prone families and individuals with multiple (>3) malignancies to discover and rigorously validate novel cancer susceptibility genes. Utilizing the resources of a major genome center, we will use tiered whole exome and full genome sequencing and filter potential candidates by a strategy including co-segregation in very large families, and comparisons to tumor derived genotypes. We will then validate findings in a separate ascertainment of >300 kindreds with no known cancer predisposing mutations. Our overall goal is to discover and validate novel genes causing increased cancer risk in clinically well-characterized families with hereditary breast, colon, hematologic and multiple-primary cancers. The discovery of new cancer susceptibility alleles will help increase the number of patients and their at-risk family members who can benefit from increased cancer surveillance, early detection and targeted cancer prevention. This project will also identify novel cancer-associated genes and pathways that may serve as future therapeutic targets.