

“Identification and Functional Analysis of Novel Cancer Susceptibility Genes in Fanconi Anemia and Familial Breast Cancer Patients”

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Abstract: Maintenance of genome stability is of utmost importance for tumor suppression. A human recessive disorder that exemplifies this principle is Fanconi anemia (FA) in which one of the 13 different genes is mutated leading to bone marrow failure and cancer predisposition, including acute myelogenous leukemia, squamous cell carcinoma of the head and neck, and cancers of the genital system and liver. The long-term objective of this project is to gain full understanding of the protein network participating in genome maintenance that fails in FA patients. Specifically, using whole exome sequencing, we will identify new germline mutations in FA patient cell lines, which do not carry a mutation in the already identified FA genes. Once identified, these genes will be further studied to deepen understanding of the FA pathway leading to better diagnosis and treatment. Since defects in the FA pathway have also been shown to be responsible for resistance to chemotherapy, understanding of the pathway is crucial to cancer therapy in the general population. Three genes that are mutated in FA patients (BRCA2, PALB2, FANCI) are also mutated in familial breast cancer predisposition syndrome patients. We have recently identified a new FA gene, which based on its activity is also a candidate to be a breast cancer predisposition gene. We will sequence this gene in a cohort of 600 patients with familial breast cancer. Once mutations are identified, they will be further studied to assess the impact of the mutations on gene function and breast cancer development.