The Paternal Germline as a Source of *de novo* Cancer Risk in Offspring

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Abstract: Inherited predisposition to the vast majority of cancers remains poorly understood. It has become clear that many disease susceptibility alleles arise *de novo* during spermatogenesis and increase in frequency, proportional to the age of the father at the time of conception. We and others have linked father's age to risk of various cancers in children, particularly leukemias and neuroblastomas. One potential mechanism for age-related increases in allele frequency is positive selection at the level of spermatogonial stem cells (SSCs), which maintain sperm production in men. The current study has three goals: (1) determine how cancer susceptibility alleles become enriched in the male germline, (2) determine the functional significance of novel cancer susceptibility alleles, and (3) develop assays for diagnosis of variants associated with *de novo* cancer risk. We will interrogate the function of candidate risk alleles identified in our whole exome sequencing (WES) studies of unaffected parents and children with early onset cancers. Specifically, Aim 1 will employ genome-editing to determine which subsets of alleles enhance SSC competitiveness. We further hypothesize that the same molecular mechanisms that confer positive selection of SSCs will also predispose offspring to tumorigenesis by increasing robustness of pre-neoplastic cells. In Aim 2, we will uncover novel pathogenic *de novo* mutations in childhood leukemias and neuroblastomas (in which we have identified a significant effect of paternal age). In Aim 3, candidate alleles from Aims 1 & 2 will undergo development of pre-clinical assays for detecting such variants in the germlines of healthy men.