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Gaps in our Knowledge of Genetics underlying Common Familial Cancer

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It has long been recognized that cancers have a familial component; some cancers more strikingly than others. This is composed of both shared genetic and environmental factors. Twin studies (monozygotic versus dizygotic) have found statistically significant effects of heritable factors in prostate (42%), colorectal (33%), and breast (27%) cancers [3]. Mendelian genetic factors account for a small proportion of these heritable factors, most notably *BRCA1* and *BRCA2*, *APC*, and the most common mismatch repair genes (*MLH1*, *MSH2*, *PMS2*, and *MSH6*). Although mutations in these genes confer a high relative risk of cancer, the fact that they are rare makes their population-attributable fraction low [2]. Case-control genome-wide association studies (GWAS) have characterized the other extreme of hereditary cancers-common genetic variants in the population which are associated with small increases in cancer risk [1]. With the GWAS, the relative risk estimates are on the order of 1.2 to 1.7, explaining only a small proportion of heritable risk. There is a large gap between these two extremes, representing 10 - 40% of the heritable risk that has yet to be defined. This is in part because cancer is a complex disease involving the interplay of multiple genetic and environmental factors. With the development of affordable whole genome sequencing technology, some of this may be teased apart in the not-so-distant future, but based on the low relative risk findings from the GWAS, its clinical utility is still in question.

The gap in understanding that requires immediate attention is the role of genetic variants that fall between the two extremes; moderately penetrant genetic variants that confer 3-fold or greater increase in relative risk. Increased cancer surveillance would be justified in this population, and like the known highly penetrant cancer genes, the molecular pathways identified may play a role in all cancers. One approach to identify moderately penetrant cancer genes is to use whole genome or exome sequencing of affected relative pairs from families with dense clustering of cancer, but without evidence of one of the known inherited syndromes. The genetic variants will likely be rare (<1% of the population) and may be unique to a family, but the genes and molecular pathways involved are likely to intersect with other families and prior knowledge to reveal true positives. When analyzing 10's of 1000's of variants coming out of this type of analysis, it is tempting (but flawed) to screen for variants that are clearly damaging. However, the moderately penetrant genetic variants probably do not damage a protein. For example, if an oncogene is involved, a non-structural amino acid change may make it slightly more active, or if a tumor suppressor is involved, it may have reduced activity or expression. Identifying these moderately penetrant genes underlying familial cancer will be challenging, but with next-generation sequencing and evolving bioinformatics resources, we now have the tools to tackle this challenge and the clinical utility is justified.

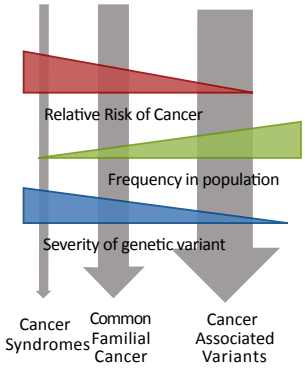

Figure 1: Inverse relationship risk, severity and frequency of a genetic mutation. The highly penetrant cancer syndromes are represented as the left arrow. The low-penetrance variants identified through GWAS are characterized by the right arrow. The gap in our knowledge is represented as the arrow between the two. The width of the arrows represents the clinically observed proportion of each diagnostic group. The red, blue, green sliders represent the lifetime relative risk of cancer, the theoretical severity, and the population frequency associated with the different classes of genetic variants respectively.

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