

GENETICS OF FAMILIAL CANCER

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The accumulating data on germline variation in various cancers are able to explain between 15 and 50% of the known familial risks. The genetic data derive essentially from 3 different sources, family studies which identified the majority of the known high-risk genes (over 110 genes), genome-wide association study (GWAS) detected genes/loci (close to 400) and finally the analysis of GWAS data for familial clustering for heritability estimates. The proportion of the 3 sources of data contributing to various cancers differs greatly. The germline architecture of breast and ovarian cancer has a major contribution from the high-risk genes while for prostate and lung cancer the major contribution is from low-risk genes. Even though the application of next-generation sequencing (NGS) has hugely increased the number of detected somatic mutations in human cancers no boost in the number of new cancer predisposing genes has been evident. Yet NGS does afford an advantageous technology also for germline sequencing. We believe that the reasons for the lack of success are manifold, including lack of appropriate families with extensive pedigrees, shortcomings in bioinformatics approaches, and, perhaps, wrong expectations about the germline architecture of human cancer. In this presentation we will compare germline approaches between GWAS and NGS technologies and describe some extensions to the existing germline genetic pipelines.

References

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