

## **GERMLINE GENETICS OF FAMILIAL CANCER**

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The presentation will start with the common definitions of population genetic parameters with examples on how familial relative risks (FRRs) of cancer can be modeled in terms of genotype relative risk, population attributable fraction (PAF) and allele frequency. The cumulated results show that the common association studies on genes with minor allele frequency >10% have power to detect disease-causing variants conferring PAFs >10%, which can be compared to known genes, such as BRCA1 with an allele frequency of 0.1% and PAF of 1.8%. Yet, common low-risk variants confer low FRRs, typically of <1.5. The models show that candidate gene studies may be able to identify genes conferring close to 100% of the PAF, but they may not explain the empirical FRRs. In order to explain FRRs, rare, high-penetrant genes or interacting combinations of common variants need to be uncovered. However, the candidate gene studies for common alleles do not target this class of genes. Next we review the estimated genetic basis of familial cancer as obtained from The Swedish Family-Cancer Database. The highest proportions of familial cancer were found for prostate (26.4%), breast (17.5%) and colorectal (15.7%) cancers. We discuss in more detail the germline genes found in these cancers and in further urological cancers. We conclude that the ever more detailed germline landscape of common cancers can be reasonably accommodated by the empirical family data on these cancers.