

Genome wide association studies for cancer

ABSTRACT:

Common cancer types aggregate in families. The discussion on the specific roles of heredity and environment in these aggregations had been restricted by the limited amount of available empiric data combined with an incomplete understanding of the tumorigenic process. Several major advances have recently provided the potential to explore a large fraction of the human genome diversity, making effective the search for association while requiring minimal functional hypotheses. Among these advances are : 1/ the realization that locus-specific relative risks are usually small and thus require in order to be detected the activation of international consortia able to pool into joint analyses large numbers of patients and controls, 2/ the establishment of the first repertoire of the human genetic diversity by the international HapMap project, 3/ the development of commercial, cost-effective semi-automated high throughput genotyping platforms. Since 2006, the genotyping of sets of DNAs on hundreds of thousand of loci has become routine practice, thus opening the Genome Wide Association Studies era. More than three hundred publications describing results of GWAS studies have now been published providing a better view on the mechanism by which genetic diversity may modulate human phenotype and disease risk.

GWAS for susceptibility to at least 18 different cancer types have been published unraveling for each of type one to a dozen susceptibility loci. Observation of multiple independent hits in the same region is not infrequent with the most striking example being a 500 kb region, in the vicinity of the MYC oncogene, which harbors multiple susceptibility loci for 4 different cancer types. Occasionally the same susceptibility locus may be shared with other trait/disease suggesting etiological relationships. Allele specific odd ratios for common cancer are usually small (i.e. less than 1.5) but may occasionally be higher for rarer forms.

There is mounting evidence that common polymorphism will only explain a small fraction of the heritability of common diseases. A complementary hypothesis posits that a substantial part of this heritability is due to many, genetically independent, rare mutations, a proposition that has recently gained experimental support.

Although some of the cancer-associated markers are located within or in proximity of genes with conspicuous functional relevance to cancer, other loci are distant from any characterized gene and the altered functions remain elusive. Taking advantage of the new generation sequencing technology, search for very rare variants in candidate functional regions may provide an effective identification strategy. Definite identification of the actual genetic variation which is directly responsible for the observed association in the initial GWAS may oppose major difficulties in the presence of strong local linkage disequilibrium.

GWAS and their follow-up studies still lack power to conclusively evaluate the role of gene/gene and gene/environment interaction in defining individual cancer risk. This lack of information obscures the delineation of the place that DNA typing will occupy in cancer prevention or early detection programs.