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SÉMINAIRE

Common cancer types aggregate in families.

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The discussion on the specific roles of heredity and environment in these aggregations has 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. 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 over twenty different cancer types have been performed unraveling for each of type one to dozens of susceptibility loci. Observations of multiple independent hits in the same region are 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 at least 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). 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. In contrast, definite identification of the actual genetic variation which is directly responsible for the observed association in the initial GWAS oppose major difficulties due to 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. .