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Relationship of intestinal- and diffuse-type gastric cancer risks to IL-10 Haplotypes and effects of radiation exposure on the relationship

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It has been reported as a result of epidemiological studies that gastric cancer risk increases in atomic-bomb (A-bomb) radiation exposures. We previously found that gene polymorphisms of IL-10, an inflammation-related cytokine, was one of the genetic factors involved in susceptibility to gastric cancer development (two major haplotype alleles, i.e., GGCG [variant] and ATTA [wild], which included IL-10 promoter regions, were strongly correlated with plasma IL-10 levels). On the other hand, it has been thought that carcinogenic pathways differ between intestinal- and diffuse-type gastric cancers. In this study, we examined risks of both intestinal- and diffuse-type gastric cancers in relation to combinations of radiation exposure dose and IL-10 haplotypes. From the Adult Health Study cohort of the Radiation Effects Research Foundation, we selected 181 cases and 1,576 controls to conduct analysis. Classification into intestinal- and diffuse-type gastric cancers was based on local cancer registry data. Written informed consent was obtained from all subjects. This study was approved by the RERF Ethical Committee for Genome Research. As a result, our analysis of relationship between the rates of the two types of cancer and radiation dose among the cases showed that the rate of the diffuse type was higher and that of the intestinal type lower among heavily exposed subjects. A multivariate analysis taking other confounding factors into account also showed that radiation exposure was involved in increased risk of diffuse-type gastric cancer but was not related significantly to risk of intestinal-type cancer. Further, we found that, in the case of the intestinal type, gastric cancer risk of unexposed people differed widely by IL-10 haplotype. We also found, however, that radiation exposure did not greatly affect cancer risks of the respective haplotypes. In contrast, in the case of the diffuse type, there was a large difference between risks by IL-10 haplotype, and radiation exposure also increased the risk especially for ATTA/ATTA. As a result, subjects exposed to high dose radiation and with variant allele GGCG showed the highest risk of gastric cancer, but variation of risk by IL-10 haplotype decreased. As shown above, past radiation exposure was related to diffuse-type gastric cancer risk. On the other hand, no significant relationship was observed for intestinal-type gastric cancer. In addition, strong correlation was found between IL-10 haplotypes and radiation for diffuse-type gastric cancer. In other words, increase in risk due to radiation exposure was marked in subjects with certain haplotypes, suggesting that there is a group of people who are genetically susceptible to radiation-related gastric cancer.

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Genome-wide identification of functional polymorphisms modulating individual risk of lung cancer

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Human lung cancer is one of the most common cancer in the world and a leading cause of cancer mortality, since it is characterized by late diagnosis and poor prognosis. Since several studies, in humans and in experimental models, suggest that genetic factors play a role in predisposition to lung cancer risk, we aimed to the identification of a genetic profile predictive of individual lung cancer risk through a genome-wide analysis of single nucleotide polymorphisms (SNPs) in Italian lung adenocarcinoma (ADCA) patients and general population controls. The analysis was performed on DNA pools using Infinium II Assay 300K on the Sentrix® BeadChip platform (Illumina), that allows for the analysis of >318,000 tag SNPs chosen from the International HapMap Project. Two independent Italian case-control series were compared and SNPs whose allele frequencies showed significant imbalances between cases and controls were further investigated. We tested putative associations by SNP analysis in the same DNA pools using an independent method (Pyrosequencing™ technology) and in the individual samples of all the series through MassARRAY® Assay (Sequenom). Genotyping in individual samples led to statistical confirmation of 8 SNPs. We found that the rare allele carrier status of all these SNPs was associated with a decreased lung ADCA risk (odds ratios from 0.6 to 0.8) and the same risk of significantly decreased by the number of rare alleles carried (P=5.3x10-9). Indeed, under a polygenic model characterized by additive and interchangeable effects, individuals carrying 2 to 6 rare alleles showed a significant trend toward a decreased risk of lung ADCA, with a strong effect for carriers of 4 or more rare alleles (OR≤0.3). These preliminary findings allowed the identification of unlinked chromosomal regions associated with lung cancer risk, suggesting that several loci are involved in the inherited modulation of lung ADCA risk, controlling susceptibility to lung cancer in humans. These loci identified by genome-wide SNP array will be investigate to assess their functional role. Of course, these results would not provide exhaustive coverage of the genetic components affecting lung cancer risk, but they represent a demonstration of the plausibility of the polygenic model in the general population and could therefore represent a first step toward the definition of a genetic profile for the estimation of individual genetic risk of lung cancer.

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BRCA1/BRCA2 mutation profile and phenotypic features of male breast cancer: a population-based study in Italy

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Male breast cancer (MBC) is a rare disease, in Italy it accounts for 0.2% of all cancers in males. Germ-line mutations of BRCA2 and, to lesser extent, BRCA1 are the highest risk factors associated with MBC. However, the frequency of BRCA1/BRCA2 mutations are quite different in ethnically diverse population- and clinic-based MBC series. In addition to point mutations, BRCA1, and at lower frequency, BRCA2 are affected by large genomic rearrangements. Interestingly, the presence of MBC seems to be the strongest predictor for the occurrence of BRCA2 rearrangements in high-risk families. In this study we performed a comprehensive analysis of BRCA1/BRCA2 point mutations and genomic rearrangements in a population-based series of 108 Italian MBCs.Deleterious point mutations were identified in 10 MBC patients (9.3%). Intriguingly, the same BRCA1 mutation (3345delAG) was identified in 2 unrelated MBC cases and haplotype analysis suggested a founder mutation. Eight MBC cases resulted BRCA2 mutation carriers. Of the 8 BRCA2 mutations, 3 were novel mutations, including a splice site variant (IVS7-2 A>G) that was shown to cause loss of exon 8 and to introduce a frameshift. In addition to pathogenetic mutations, 2 novel missense unclassified BRCA2 variants (K382N and Q2829K) were identified. A pathogenetic effect for the BRCA2 K382N variant was suggested by additional analyses.No BRCA1/BRCA2 genomic rearrangements were detected by using MLPA in MBCs negative for BRCA1/BRCA2 mutations, thus indicating that screening of large BRCA1/2 rearrangements is not to be recommended in unselected MBC cases.The immuno-phenotypic parameters of tumours, including ER, PR, MIB1 and HER-2 were examined: 88% of MBCs resulted positive for ER, 80.4% for PR, 32.2% for MIB1 and 17.8% for HER-2. Interestingly, a statistically significant association emerged among BRCA2 mutations and HER-2 expression (p=0.019).Study supported by AIRC (Associazione Italiana per la Ricerca sul Cancro) to L.O.

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Polymorphisms in predicted microRNA binding sites in integrin genes and breast cancer- ITGB4 as prognostic marker

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It is well-established that genetic variation in addition to the mutations in the known breast cancer (BC) susceptibility genes BRCA1 and BRCA2 affect individual's risk of BC. Recently, it has become increasingly clear that also survival in BC has an inherited component. While cancer risk is related to defects in cell cycle control and DNA integrity, survival is dependent on tumor progression and metastasis. Integrins control the cell attachment to the extracellular matrix and play an important role in mediating cell proliferation, migration and survival. A number of important cancer-associated integrin genes can be regulated by microRNAs (miRNAs) that bind to their target sites in the 3´ untranslated regions (UTRs). Genetic variation in the regulatory 3´UTR of the integrin genes may affect gene expression and thus BC susceptibility as well as tumor aggressiveness and survival of the BC patients. We investigated the effect of single nucleotide polymorphisms (SNPs) in the 3´UTRs of six integrin genes (ITGA3, ITGA6, ITGAv, ITGB3, ITGB4, ITGB5) on BC risk, clinical tumor characteristics and patient survival.

Six SNPs were genotyped in 749 Swedish incident BC cases with detailed clinical data and up to 15 years of follow-up together with 1493 matched controls. We evaluated associations between genotypes and BC