Contribution of DNA repair-related genetic polymorphisms to papillary thyroid carcinoma susceptibility in Belarusian children exposed to radiation

Fabienne Lesueur[1§], Francesca Damiola[2], Christine Lonjou[1], Monika Moissonnier[3], Geoffroy Durand[4], Vanessa Tenet[5], Irina Malakhova[6], Vladimir Masyakin[7], Florence Le Calvez-Kelm[4], Elisabeth Cardis[8], Graham Byrnes[9], Ausrele Kesminiene[3]

[§]Presenting author

[1] INSERM, U900, Institut Curie, Mines ParisTech, 75248 Paris, France.
[2] CRCL, CNRS UMR5286, INSERM U1052, Centre Léon Bérard, Lyon, France.
[3] Environment and Radiation, International Agency for Research on Cancer (IARC), 69372 Lyon, France.
[4] Genetic Cancer Susceptibility, IARC, 69372 Lyon, France.
[5] Infections and Cancer Epidemiology, IARC, 69372 Lyon, France.
[6] Republican Scientific and Practical Center for Medical Technologies, Informatisation, Administration and Management of Health (RSPC MT), 220013 Minsk, Belarus.
[7] Republican Research Center of Radiation Medicine & Human Ecology, 246040 Gomel, Belarus.
[8] Centre for Research in Environmental Epidemiology (CREAL), IMIM (Hospital del Mar Research Institute), CIBER Epidemiología y Salud Pública (CIBERESP), 08003 Barcelona, Spain.
[9] Biostatistics, IARC, 69372 Lyon, France.

Abstract

Background

After the Chernobyl nuclear power plant accident in April 1986, a dramatic increase in the incidence of thyroid cancer, virtually all papillary Thyroid Carcinoma (PTC) was observed in children living in the contaminated areas of Belarus, Ukraine and Russian Federation. The familial aggregation of thyroid diseases and thyroid cancer, even in the presence of widely varying radiation doses, suggests that genetic factors may contribute to the risk of PTC. Indeed, linkage analyses in PTC families identified several putative loci, and association studies, using either genome-wide or based on candidate approaches, have reported an association between several Single Nucleotide Polymorphisms (SNPs) and the risk of PTC in the absence of radiation.

Objective

Since the inter-individual variability in response to radiation exposure have been observed, we seek to investigate how environmental and host factors interplay to modify PTC risk in Belarusian children exposed to radiation.

Methods

A set of 165 common SNPs that had been previously associated with PTC (19 SNPs) or that are located in DNA repair genes (146 SNPs) was genotyped in 82 PTC cases and 325 population controls matched to cases for age at the time of accident, sex, and type of settlement. The studied population corresponds to a sub-group of subjects from the population-based case-control study carried out at the IARC in the most contaminated areas of Belarus to evaluate the risk of thyroid cancer after exposure to radioactive iodine in childhood. All genotyped subjects are from the Gomel region in Belarus, and were younger than 15 years at the time of the Chernobyl accident. Conditional logistic regressions accounting for radiation dose were performed with PLINK using the additive allelic inheritance model. A combined p-value for the joining effects of all markers

within a gene was calculated using the rank truncated product method. Statistical significance was evaluated empirically by permutation.

Results

Among the tested SNPs that had been associated with PTC risk in other populations, significant association was found for rs1867277 in the promoter of *FOXE1* (per minor allele odds ratio OR=1.55, 95% CI 1.03, 2.34), a gene involved in thyroid development, differentiation and regulation of thyroid function, and for rs1801516 (D1853N) in the DNA damage recognition gene *ATM* (OR=0.34, 95%CI 1.03, 2.34). To follow up with this findings we further explored the role of SNPs in DNA repair genes acting downstream of ATM in the same population. The intronic SNP rs2296675 in the methyltransferase gene *MGMT* was significantly associated with an increased PTC risk (OR=2.44, 95%CI 1.47, 4.04, P=0.00039). This association remained significant after adjusting for multiple testing (P_{perm}=0.001). Suggestive association was also found for SNPs rs1047768 in *ERCC5*, (P_{perm}=0.03), rs17349 in *PCNA* (P_{perm}=0.04), and rs1051685 in *XRCC5* (P_{perm}=0.07).

Conclusions

In addition to *FOXE1*, a gene that has been recurrently associated with PTC risk in different populations, our results support the involvement of several DNA repair genes acting in distinct functional modules in PTC susceptibility, and investigation of the functional properties of these genes may further enhance our understanding about the aetiology of this cancer. Moreover, we showed that the studied genetic polymorphisms and radiation dose appear to act as independent multiplicative factors for PTC.