1. Background

Although somatic mutations in the Janus kinase 2 gene (JAK2) occur in many Philadelphia-chromosome negative chronic myeloproliferative neoplasms (PN-PMNs), disease evolution, distinct phenotypes and the continuous clinical evidence of an increasing number of cases, with younger patients affected, have been pointing to a growing involvement of environmental factors in the pathogenesis of these diseases. Although this association is well established in some solid tumors, like breast and thyroid, this aspect is now being considered for hematological malignancies. Exposure to hazardous agents in the environment on a continual basis, can lead to changes at the genome level, alterations in cell cycle regulation and consequently to cancer. Single nucleotide polymorphisms (SNPs) have been identified, that may influence the DNA repair capacity and, in turn, confer genetic predisposition to disease and determine therapeutic response (e.g. DNA repair, apoptosis).

On the other hand, the phenotypic pleiotropy of these disorders seems to be the result of a combination of somatic mutation(s), inherited genetic variability, post-genetic regulation and host modifiers (Fig. 1).

2. Objectives

We intend to evaluate the role of base excision repair (BER) pathway SNPs in PN-PMNs susceptibility.

3. Methods

We performed a case-control study in 121 Caucasian Portuguese PN-PMNs patients (73 with Essential thrombocytopenia ET, 35 with Polycythemia vera (PV) and 13 with Idiopathic Myelofibrosis (IMF)) and 280 matched controls. Most of the patients were diagnosed and are followed by some of the elements of this working group, r1799782 and r25487 (XRCC1), r1052131 (OGG1), r1136410 (PARP1), r134282 and r2050112 (PARP4), r1133409 (APEKX) and r32118489 (MUTHY) were genotyped using real-time PCR (RT-PCR 7300 Applied Biosystems), through TaqMan® SNP genotyping assays (Life Technology), according to manufacturer instructions. Differences in genotype frequency, smoking status, age class, gender and pathology distribution between patients and controls were evaluated using SPSS 22.0 (SPSS Inc.).

4. Results

When considering all PN-PMNs cases, r1799782 (XRCC1_194) was associated with MPNs risk. A consistent increase in overall PN-PMNs risk was observed for the presence of at least one variant allele carriers (Arg/Trp or Trp/Trp; OR=2.2, 95% CI=1.3-3.5), more significant between women (Tables 1 and 2). Although variation in smoking status, age class, gender and pathology distribution between patients and controls were evaluated using SPSS 22.0 (SPSS Inc.).

Concerning pathology stratification, IMF did not show an increased risk in association with this polymorphism. JAK2V617F positive cases revealed a borderline effect for the presence of at least one variant allele carriers of XRCC1_194 (OR=1.8, 95% CI=0.8-3.4, P=0.059).

Results for PARP4_13 were not shown, since it is in linkage disequilibrium with PARP4_01. Our data still reveal to posit a positive association between the other polymorphisms individually and PN-PMNs susceptibility. Studies related with therapeutic response are still ongoing.

5. Conclusions

Our results suggest that BER polymorphisms such as r1799782 (XRCC1_194) may influence PN-PMNs susceptibility. The more significant association between women can be due to the predominance of ET cases, which has been referred in the literature as having a slight female sex predilection. On the other hand, the lack of association in IMF cases can be due to the small sample size. However, larger studies are required to confirm these results and to provide conclusive evidence of association between these and other BER variants and PN-PMNs and therapeutic response.

6. References


**Table 2** – ORs (95% CI) for XRCC1_194 (Arg14Trp) polymorphism and PN-PMNs association.

**Table 1** – General characteristics for the PN-PMNs cases (n=121) and control population (n=280).

**Table 3** – Characteristics for the PN-PMNs cases (n=121) and control population (n=280).