THE ROLE OF BASE EXCISION REPAIR POLYMORPHISMS IN INDIVIDUAL SUSCEPTIBILITY TO PHILADELPHIA-NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

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1. Background

Although somatic mutations in the Janus kinase 2 gene (*JAK2*) occur in many Philadelphia-chromosome negative chronic myeloproliferative neoplasms (PN-MPNs), 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. Several 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).

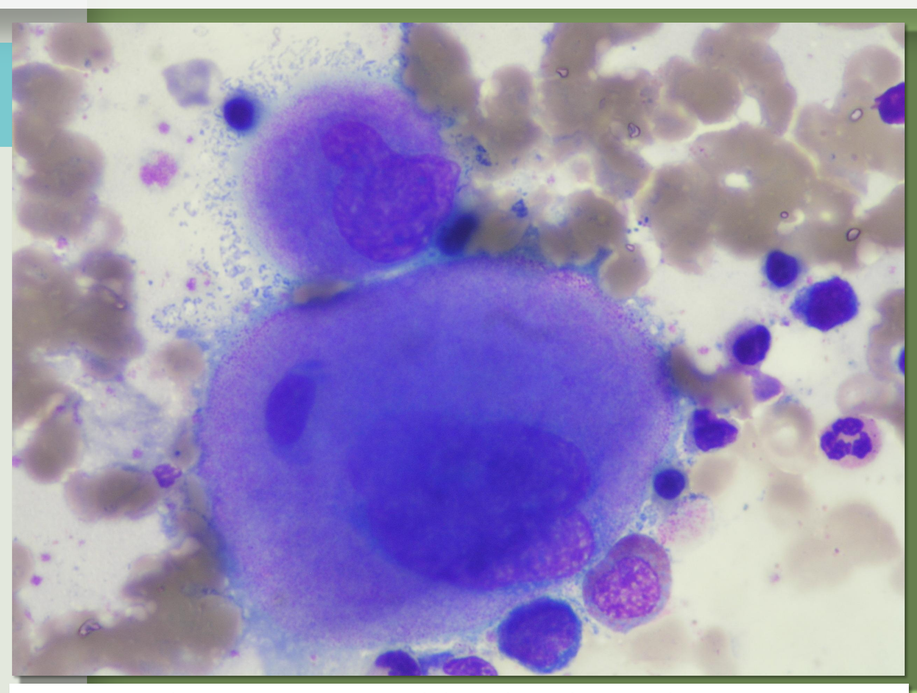

Fig. 1 – Megakaryocytes in essential thrombocythaemia, bone marrow aspirate smear (x100).

2. Objectives

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

3. Methods

We performed a case-control study in 121 Caucasian Portuguese PN-MPNs patients (73 with Essential thrombocythaemia (ET), 35 with Polycythaemia vera (PV) and 13 with Idiopatic Myelofibrosis (IMF)) and 280 matched controls. Most of the patients were diagnosed and are followed by some of the elements of this working group. rs1799782 and rs25487 (*XRCC1*), rs1052133 (*OGG1*), rs1136410 (*PARP1*), rs13428 and rs1050112 (*PARP4*), rs1130409 (*APEX1*) and rs3219489 (*MUTYH*) were genotyped using real-time PCR (RT-PCR 7300 Applied Biosystem), through TaqMan® SNP genotyping assays (Life Technology), according to manufacturer instructions.

Differences in genotype frequency, smoking status, age class, gender and pathology distributions between patients and controls were evaluated using SPSS 22.0 (SPSS Inc.).

4. Results

When considering all PN-MPNs cases, rs1799782 (*XRCC1_194*) was associated with MPNs risk. A consistent increase in overall PN-MPNs risk was observed for the presence of at least one variant allele carriers (Arg/Trp or Trp/Trp; OR=2.2, 95% CI=1.4-3.5), more significant between women (Tables 1 and 2).

It seems that alcohol consumption also increases the risk for PN-MPNs development.

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=0.98-3.4, *P*=0.059).

Results for *PARP4_13* were not shown, since it is in linkage disequilibrium with *PARP4_01*. Our data did not reveal a positive association between the other polymorphisms individually and PN-MPNs susceptibility.

Studies related with therapeutic response are still ongoing.

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

Characteristics	Cases, *n* (%)	Controls, *n* (%)	*P* value
Gender			
Male	56 (29.6)	133 (70.4)	0.8
Female	65 (30.7)	147 (69.3)	
Age [a, b]			0.9
30-49	16 (27.1)	43 (72.9)	
50-69	47 (30.5)	107 (69.5)	
≥70	58 (30.9)	130 (69.1)	
Smoking habits			0.9
Never	93 (30.5)	212 (69.5)	
Current	28 (29.5)	67 (70.5)	
Alcohol habits			**<0.0001**
Never	92 (32.6)	190 (67.4)	
Social	20 (44.4)	25 (55.6)	
Regular	9 (12.3)	64 (87.7)	
MUTYH (Gln335His)			0.7
Gln/Gln	13 (36.1)	23 (63.9)	
Gln/His	47 (29.6)	112 (70.4)	
His/His	61 (30.2)	141 (69.8)	
APEX1 (Asp148Glu)			0.9
Asp/Asp	34 (31.8)	73 (68.2)	
Asp/Glu	57 (29.7)	135 (70.3)	
Glu/Glu	30 (30.6)	68 (69.4)	
OGG1 (Ser326Cys)			0.6
Ser/Ser	76 (29.6)	181 (70.4)	
Ser/Cys	37 (30.8)	83 (69.2)	
Cys/Cys	8 (40.0)	12 (60.0)	
PARP1 (Val762Ala)			0.7
Val/Val	96 (31.1)	213 (68.9)	
Val/Ala	25 (28.4)	63 (71.6)	
Ala/Ala	0 (0.0)	1 (100.0)	
PARP4_01 (Gly280Arg)			0.6
Gly/Gly	48 (31.4)	105 (68.6)	
Gly/Arg	56 (28.6)	140 (71.4)	
Arg/Arg	17 (35.4)	31 (64.6)	
XRCC1_399 (Gln399Arg)			0.7
Gln/Gln	15 (34.1)	29 (65.9)	
Gln/Arg	54 (28.7)	134 (71.3)	
Arg/Arg	52 (31.5)	113 (68.5)	
XRCC1_194 (Arg194Trp)			**<0.0001**
Arg/Arg	77 (26.1)	218 (73.9)	
Arg/Trp	28 (33.3)	56 (66.7)	
Trp/Trp	16 (94.1)	1 (5.9)	

[a] Age of diagnosis for cases

[b] Age of control population at the time of diagnosis for the matched case

Table 2 – ORs (95% CI) for *XRCC1_194* (Arg194Trp) polymorphism and PN-MPNs association.

	n	*XRCC1_194* (Arg194Trp)	OR crude (95% CI)	OR adjusted (95% CI)[a]
All cases	121	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp	1.4 (0.8-2.4)	1.5 (0.9-2.5)
		Trp/Trp	45.3 (5.9-347.3)[c]	40.1 (5.2-309.9)
		Arg/Trp or Trp/Trp	2.2 (1.4-3.5)*	2.3 (1.4-3.7)*
Gender				
Male	56	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp or Trp/Trp	1.8 (0.96-3.4)	2.1 (1.1-4.1)*
Female	65	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp or Trp/Trp	2.6 (1.4-4.5)*	2.7 (1.5-4.9)*
Pathology stratification				
ET	73	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp or Trp/Trp	2.4 (1.4-4.1)*	2.5 (1.4-4.4)*
PV	35	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp or Trp/Trp	2.6 (1.2-5.3)*	2.7 (1.3-5.8)*
CIM	13	Arg/Arg[b]	1 (Reference)	1 (Reference)
		Arg/Trp or Trp/Trp	0.7 (0.2-3.2)	0.9 (0.2-4.5)

[a] ORs were adjusted for age (30-49, 50-69 and ≥70), smoking status (never and current)

[b] The individuals with Arg/Arg genotype were considered as reference class

[c] Statistical error type 1 ; * $P < 0.05$

5. Conclusions

Our results suggest that BER polymorphisms such as rs1799782 (*XRCC1-194*) may influence PN-MPNs 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-MPNs and therapeutic response.

6. References

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