Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome: is PTPN22 involved?

Sirs,

The aetiology of Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome has been debated since its first description in 1987 (1-4) and controversy has existed as to whether the categorisation of SAPHO syndrome as a distinct disease is appropriate (2, 3). To date, there is increasing evidence that SAPHO syndrome may be a multifactorial auto-inflammatory disorder, resulting from complex interactions between a number of predisposing factors and a variety of exogenous factors that trigger, accelerate or exacerbate the disease (5). Studies of class II HLA antigens have revealed no role for HLA-B27, Cw6 and other psoriasis or psoriatic arthritis susceptibility genes (1, 2, 6).

We report the results of a case control analysis aiming to investigate whether the genetic component of SAPHO syndrome could be disclosed by *PSTPIP2*, *LPIN2*, *NOD2* as well as *PSTPIP1* or *PTPN22* single nucleotide polymorphisms (SNPs). This study was approved by the Human Studies Committee of the Azienda Ospedaliera-Universitaria Sant'Anna (Ferrara). Informed written consent was obtained from all the participants.

In the 5 abovementioned genes, we interrogated 22 SNPs possibly associated to other auto-inflammatory disorders, in DNA samples from 53 apparently unrelated individuals previously reported for SAPHO syndrome (1), and from 150 control samples (113 females, 37 males, >18 years old, born in Emilia-Romagna, the same region of origin as the cases).

With such a sample size, we calculated that only a SNP with minor allele frequency (MAF) >0.15 and odds ratio (OR) >2.5 could achieve statistical power of 80% under an additive model (7). All the SNPs with missing genotype rate <0.25, MAF >0.001, Hardy-Weinberg equilibrium (HWE) *p*-value >0.001 and pair-wise r^2 <0.8 were retained in the study. We performed allelic association analysis calculating chi-square, Fisher's exact tests and OR with confidence interval (C.I.) 0.95. *P*-values were corrected according to Bonferroni.

Only 2 SNPs in *PTPN22* showed significant *p*-values at the 0.05 level. However, none of them remained after Bonferroni correction (Table I).

Table I. Results of the SNP association analysis.

GENE	CHR	SNP	Variant	Allele	Allele frequency (cases/controls)	*p*-value (corrected)	*p*-value Fisher	OR (95% CI)
PTPN22	1	rs3811021	c.*864T>C	C	0.201/0.097	0.006(0.132)	0.009	2.33 (1.25–4.32)
PTPN22	1	rs2476601	c.1858C>T (p.Arg620Trp)	C	0.982/0.927	0.043(0.946)	0.030	0.24 (0.56–1.06)

In conclusion, we interrogated SNPs in 3 genes (*PSTPIP2*, *LPIN2* and *NOD2)* previously analysed in a cohort of 38 French patients (8), as well as in 2 genes (*PSTPIP1* and *PTP*N22) which we looked at for the first time. The same as for the French cohort, no SNP was found in association to SAPHO syndrome in our Italian cohort of 53 patients.

The highest divergence in frequency between cases and controls was observed for SNP rs3811021, which is suspected to predispose to rheumatoid arthritis (RA) (9). *PTPN22* is a reasonable candidate for SAPHO syndrome and further studies may attempt to replicate our findings in another population of similar genetic background. Our restricted cases/controls cohort did not allow for a significant statistical achievement. No independent sample was available to replicate our findings. *PTPN22* allele frequencies are known to vary widely across different Italian regions, and recent migratory events might have contributed to introduce stratification in the Italian population. For this reason we recruited controls born in the same region of origin of patients, in an attempt to avoid stratification.

Our results, which reflect differences in cases/controls allele frequencies in a small cohort of cases affected with a very rare multi-factorial syndrome, may deserve attention even if not statistically significant.

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