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Letter to the Editor

Lack of association between the *TNFAIP3* rs2230926 variant and rheumatoid arthritis-associated lymphoma

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There is an increased risk of lymphoma in patients with autoimmune diseases (AID) especially rheumatoid arthritis (RA) and primary Sjögren Syndrome (pSS) with a respective relative risk of 2 and 15 [1]. The mechanisms promoting lymphomagenesis in AID might be diverse [2]. Disease activity and chronic antigenic stimulation of autoimmune B cells play a key role in lymphomagenesis associated with pSS [3]. In this context, a complete control of the NF-kB pathway activation is required to avoid B-cell clonal proliferation. *TNFAIP3* encodes for the protein A20, a key gatekeeper of NF-kB activation and the *TNFAIP3* rs2230926 variant was previously found to be associated with lymphoma in pSS [4,5]. This variant is responsible for a slight decreased control of NF-kB activation. In patients with RA, mechanisms leading to lymphoma occurrence, mainly diffuse large B-cell lymphoma (DLBCL), is less understood. From an epidemiologic point of view, it has been demonstrated that high cumulative RA disease activity increase odds for lymphoma [6]. Given the association of *TNFAIP3* rs2230926 with the overall RA [7], and pSS-related lymphoma [4,5], we decided to investigate its contribution to RA-related lymphoma susceptibility.

To this end, a multicentre case-control study was performed. Cases were patients with RA fulfilling ACR-EULAR 2010 criteria, who developed a B-cell NHL or Hodgkin's lymphoma after the diagnosis of RA. Controls were patients with RA and without lymphoma matched on age. Fifty-four cases of RA-related lymphoma were included and matched to 108 controls (1:2) [8]. DNA was available for 145/162 (89.5%) patients (38 cases and 107 controls), having no difference in demographic and disease characteristics compared to the whole study population (Table 1). Overall, 101 patients (69.2%) were female, with a mean age of 51.9 years (SD = 10.9) at RA diagnosis and a mean disease duration of 10.5 years (SD = 4.9). Lymphomas were mostly DLBCL ($n = 19$, 50.0%), follicular lymphoma ($n = 6$, 15.8%) and marginal zone lymphoma ($n = 4$, 10.5%). The genotyping study revealed no significant association between the *TNFAIP3* rs2230926 variant and the occurrence of lymphoma ($P = 0.30$) (Table 2).

Even if this study could suffer from a relatively low power of detection (estimated power of 80%), this lack of association suggests distinct mechanisms of lymphomagenesis in RA and pSS.

Table 1
characteristics of the genotyping study population.

	Whole genotyping study population ($n = 145$)	Cases ($n = 38$)	Controls ($n = 107$)
Male gender, *n* (%)	45 (31.0)	20 (52.6)	25 (23.4)
Age at RA diagnosis, mean (SD)	51.9 (10.9)	49.8 (12.6)	52.7 (10. 2)
Age at the time of matching, mean (SD)	62.0 (10.1)	61.2 (10.2)	62.2 (10.1)
ACPA positivity, *n* (%)	106 (73.1)	35 (92.1)	71 (66.4)
RF positivity, *n* (%)	111 (76.6)	35 (92.1)	76 (71.0)
Erosions on X-rays at the time of matching, *n* (%)	55 (37.9)	30 (78.9)	25 (23.4)
DAS28 at the time of matching, mean (SD)	2.9 (1.5)	3.9 (1.7)	2.6 (1.4)
RA duration at the time of matching, mean (SD)	10.6 (5.0)	11.9 (9.7)	10.0 (0.3)
Year of RA diagnosis, median (IQR)	2002 (1978–2016)	2000 (1978–2016)	2004 (2002V2005)
Year of lymphoma diagnosis/10-year ESPOIR visit, median (IQR)	2013 (1996–2018)	2012 (1996–2018)	2014 (2012–2015)

IQR: interquartile range; ACPA: anti-citrullinated peptide antibodies; DAS28: disease activity score in 28 joints; RA: rheumatoid arthritis; RF: rheumatoid factor; the time of matching corresponded to the diagnosis of lymphoma for cases and the 10-year ESPOIR visit for controls.

Table 2
Testing for association of *TNFAIP3* rs2230926 with RA-related lymphoma.

TNFAIP3 rs2230926	Cases ($n = 38$)	Controls ($n = 107$)	OR (95% CI)
MAF	2.6%	5.6%	0.45 (0.10–2.08)
TT	36 (94.7%)	96 (89.7%)	0.49 (0.10–2.30)
TG	2 (5.3%)	10 (9.3%)	0.53 (0.11–2.55)
GG	0 (0.0%)	(0.9%)	-

MAF: minor allele frequency. Chi-square test. Differences between cases and controls were statistically non significant.

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Lymphoma histology and localization differ in pSS and RA associated lymphoma: MALT lymphoma of salivary glands in pSS versus nodal DLBCL in RA. RF positivity and/or cryoglobulinemia are associated with lymphoma occurrence in pSS but not in RA [3]. In RA, instead of a direct transformation of autoimmune B cells, lymphoma might derive from associated subsets of B cells such as memory B cells. Interestingly, memory B cells involved in RA are increased in longstanding disease [9]. Recently, *TBL1XR1* rare variants were found to induce ABC DLBCL by promoting aberrant memory B cells, which are prone to avoid plasmocytic differentiation on recall and to undergo systemic dissemination [10].

In aggregates, we did not detect any association between the *TNFAIP3* rs2230926 variant and RA-related lymphoma. This highlights the need for further studies to determine the specific mechanisms driving RA lymphomagenesis.

Disclosure of interest

The authors declare that they have no competing interest.

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Espoir cohort

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Contributorship statement

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