Response to: 'NCF1-339 polymorphism and systemic lupus erythematosus' by Joob and Wiwanitkit

In the comment by Joob and Wiwanitkit,¹ questions are raised regarding the role of the NCF1-339 rs201802880 polymorphism in systemic lupus erythematosus (SLE) in our recent publication.² One concern relates to the possibility of a molecular weight change due to the polymorphism and if this could alter phenotypic expression. Studies of functional effects of the polymorphism in question have been demonstrated both in this report as well as in earlier work by our group.^{3,4} NCF1 (p47^{phox}) plays a vital role in the assembly and stability of the extensively studied nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 complex⁵ and the nucleotide shift from C to T at NCF1-339 alters the amino acid from arginine to histidine at a PX domain of the NCF1 protein.⁶ This domain has been shown to be of crucial importance in the membrane binding and mutations in the NCF1-339 position reduces reactive oxygen species (ROS) response,^{4,7} providing a mechanistic explanation for the observed ROS-decreasing effect of the polymorphism. We have not considered comparing molecular weight of polymorphic NCF1 and non-polymorphic molecules. Placing a polymorphism in a functional context provided by current and previous findings is far more relevant in our opinion. We find it unlikely that a potential molecular weight difference would add any significant information relevant to the biological/pathological context presented.

A second concern was raised about the potential role of other polymorphisms and possible functional consequences. Joob and Wiwanitkit are particularly interested in the putative effects of polymorphisms in the paraoxonase-1 gene and PAL-1. Our aim with this study was to determine the functional effect of NCF1-339 polymorphisms on neutrophil extracellular traps, type I interferon activity and to find potential associations with clinical phenotypes in SLE. The striking association between NCF1-339 polymorphisms and the antiphospholipid syndrome does not exclude associations with other polymorphisms but this was beyond the scope of this investigation.

Carl Petrus Linge , Anders Bengtsson

Correspondence to Dr Carl Petrus Linge, Department of Clinical Sciences, Section of Rheumatology, Faculty of Medicine, Lund University, Lund, Sweden; petrus.linge@med.lu.se

Handling editor Josef S Smolen

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Linge CP, Bengtsson A. *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2019-216669

Received 26 November 2019

Revised 29 November 2019

Accepted 30 November 2019

► <http://dx.doi.org/10.1136/annrheumdis-2019-216669>

Ann Rheum Dis 2019;0:1. doi:10.1136/annrheumdis-2019-216669

ORCID iD

Carl Petrus Linge <http://orcid.org/0000-0001-8906-2715>

REFERENCES

- Joob B, Wiwanitkit V. NCF1-339 polymorphism and systemic lupus erythematosus. *Ann Rheum Dis* 2019. doi:10.1136/annrheumdis-2019-216629. [Epub ahead of print: 28 Nov 2019].
- Linge P, Arve S, Olsson LM, et al. NCF1-339 polymorphism is associated with altered formation of neutrophil extracellular traps, high serum interferon activity and antiphospholipid syndrome in systemic lupus erythematosus. *Ann Rheum Dis* 2019. doi:10.1136/annrheumdis-2019-215820. [Epub ahead of print: 08 Nov 2019].
- Olsson LM, Johansson Åsa C, Gullstrand B, et al. A single nucleotide polymorphism in the NCF1 gene leading to reduced oxidative burst is associated with systemic lupus erythematosus. *Ann Rheum Dis* 2017;76:1607–13.
- Olsson LM, Nerstedt A, Lindqvist A-K, et al. Copy number variation of the gene NCF1 is associated with rheumatoid arthritis. *Antioxid Redox Signal* 2012;16:71–8.
- Thomas DC. The phagocyte respiratory burst: historical perspectives and recent advances. *Immunol Lett* 2017;192:88–96.
- Zhong J, Olsson LM, Urbanaviciute V, et al. Association of Nox2 subunits genetic variants with autoimmune diseases. *Free Radic Biol Med* 2018;125:72–80.
- Li XJ, Marchal CC, Stull ND, et al. P47Phox phox homology domain regulates plasma membrane but not phagosome neutrophil NADPH oxidase activation. *J Biol Chem* 2010;285:35169–79.