Correspondence on 'NCF1-339 polymorphism is associated with altered formation of neutrophil extracellular traps, high serum interferon activity and antiphospholipid syndrome in systemic lupus erythematosus' by Linge *et al*

We read with great interest the article by Linge *et al*[1] on 'NCF1-339 polymorphism is associated with altered formation of neutrophil extracellular traps, high serum interferon activity and antiphospholipid syndrome in systemic lupus erythematosus'[1] as well as the response of Linge and Bengtsson[2] to the comment by Joob and Wiwanitkit,[3] who raised a question regarding the importance and the role of the NCF1-339 rs201802880 (p. Arg90His) polymorphism in systemic lupus erythematosus (SLE). Linge and Bengtsson[3] nicely placed this polymorphism in a functional context, pointing out that the amino acid shift from arginine to histidine at a PX domain of the NCF1 protein (a domain of crucial importance in the membrane binding[4] reduces reactive oxygen species (ROS) response.[5] Of note, the rs201802880 p. Arg90His variant of he *NCF1* gene has been associated, apart from SLE, with rheumatoid arthritis and Sjögren's syndrome in adult patients[6] as well as with early-onset interferonopathy in paediatric patients.[7]

Our aim with this letter was to extend the information given by Linge and Bengtsson[3] by presenting data that elucidate further the significance of the rs201802880 Arg90His variant from another viewpoint, using data from a structural biology approach, thus analysing this variant in the various genetically controlled functions that is involved, including the neutrophil extracellular trap formation, the reduced extracellular ROS production in neutrophils and the decreased NADPH oxidase function.[1] To this end, we have recently evaluated the structural significance of the rs201802880 variant on the $p47^{phox}$ PX domain of the NCF1 protein by constructing a three-dimensional structural model, focusing on the phosphate-binding pocket of NCF1 $p47^{phox}$ domain with the electrostatic molecular surface.[8] Our molecular investigation showed that in this variant, the functionality of the $p47^{phox}$ PX cytosolic subunit of neutrophil NADPH oxidase has been modified, leading to affinity reduction to PtdIns(3,4)P2 caused by the loss of specific phosphoinositide head group interactions and affecting the $p47^{phox}$ translocation to the plasma membrane.

The structural biological information reported here may help the interpretation of the findings of Linge *et al*[1] from the structural–functional point of view and, apparently, is in agreement with the statements in the comment of Linge and Bengtsson[3] that emphasise on the crucial importance of the NCF1- 339 polymorphism under discussion.

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