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Pedersen, Kasper Mønsted; Çolak, Yunus; Hasselbalch, Hans Carl; Bojesen, Stig Egil; Nordestgaard, Børge Grønne

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## Letter

## Tocilizumab and soluble interleukin-6 receptor in *JAK2V617F* somatic mutation and myeloproliferative neoplasm

Kasper Mønsted Pedersen<sup>a,b,c</sup>, Yunus Çolak<sup>a,b,c</sup>, Hans Carl Hasselbalch<sup>c,d</sup>, Stig Egil Bojesen<sup>a,b,c</sup>, Børge Grønne Nordestgaard<sup>a,b,c,\*</sup>

<sup>a</sup> Department of Clinical Biochemistry, Copenhagen University Hospital, Herlev and Gentofte Hospital, Herlev, Denmark

<sup>b</sup> The Copenhagen General Population Study, Copenhagen University Hospital, Herlev and Gentofte Hospital, Herlev, Denmark

<sup>c</sup> Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

<sup>d</sup> Department of Haematology, Zealand University Hospital, Roskilde and Køge Hospital, Roskilde, Denmark

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## From the authors

We thank Drs. Garbers and Rose-John for their interest in our study, where we found that a loss-of-function polymorphism in the interleukin-6 receptor (*IL6R*) gene reduces risk of the *JAK2V617F* somatic mutation and myeloproliferative neoplasm [1]. They raise some interesting points related to the underlying mechanism of soluble *IL6R* (s*IL6R*) and its relationship with tocilizumab treatment, a monoclonal antibody that targets the *IL6R* [2].

We used the genetic polymorphism rs4537545 that is in high linkage disequilibrium with rs2228145 in the *IL6R* gene, which causes the non-synonymous exchange of Asp-358 to Ala-358 in the *IL6R* protein. This results in reduced membrane-bound *IL6R* due to increased proteolytic cleavage followed by increased s*IL6R* concentration [1,3]. This blocks the classical signalling pathway of *IL6R* and thereby dampens inflammation. Indeed, as emphasized by Garbers and Rose-John, increased s*IL6R* in combination with soluble glycoprotein-130 in the blood circulation can act as a natural buffer that can neutralize *IL6*, thereby also dampen inflammation [1,4,5].

We agree that tocilizumab treatment, with reservations to its pharmacokinetic properties, will potentially block all s*IL6R* molecules thereby rendering them biologically inactive. In contrast, s*IL6R*

molecules in individuals with genetic polymorphism in *IL6R* are fully biologically active. Although the two scenarios may not be fully comparable, it does not change the notion that treatment with tocilizumab and other agents that target the same inflammatory pathway such as canakinumab, a monoclonal antibody that targets the more central regulator interleukin-1 $\beta$ , could potentially be considered as candidate drugs for myeloproliferative neoplasms.

## Declaration of Competing Interests

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\* Corresponding author: Børge G. Nordestgaard, MD, DMSc, Professor, Chief Physician, Department of Clinical Biochemistry, Copenhagen University Hospital, Herlev and Gentofte Hospital, Borgmester Ib Juuls Vej 1, Entrance 7, 4. Floor, N5, DK-2730 Herlev, Denmark. Phone: +45 38683297, Fax: +45 38683311.

E-mail address: [Boerge.Nordestgaard@regionh.dk](mailto:Boerge.Nordestgaard@regionh.dk) (B.G. Nordestgaard).

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