Genetic polymorphisms, vitamin D binding protein and vitamin D deficiency in COVID-19

To the Editor:

With interest, we read the paper of Faniyi *et al.* [1], which investigated the relationship between vitamin D status and seroconversion for coronavirus disease 2019 (COVID-19) in UK healthcare workers. More specifically, vitamin D deficiency was an independent risk factor for the development of COVID-19 seroconversion, with the biggest differences seen in the Black, Asian and minority ethnic (BAME) male group. Although several comorbidities were taken into account, we would like to highlight the importance of vitamin D binding protein (DBP) and its polymorphism in the interpretation of low 25-hydroxyvitamin D (25(OH)D) levels in the BAME population with COVID-19.

DBP, a serum 2-globulin of 52–59 kDa, is the major binding/transport protein of all vitamin D metabolites with a single binding site. Total 25(OH)D is defined by the DBP-bound fraction (approximately 85–90% of total 25(OH)D), the albumin-bound fraction (10–15% of total 25(OH)D), and the free circulating fraction (<1% of total 25(OH)D). The access of all vitamin D metabolites to cells and tissues is regulated by DBP [2]. Apart from its specific sterol-binding capacity, DBP exerts several other important biological functions, such as actin scavenging, fatty acid transport, macrophage activation and chemotaxis [3].

There is a well-documented genetic polymorphism of DBP, characterised by three frequent alleles (DBP1F (fast), DBP1S (slow), and DBP2), and by a large number (>124) of variants. Using isoelectric focusing, DBP1F proteins have a slightly faster electrophoretic mobility in comparison with DBP1S proteins. Two polymorphisms in the *DBP* gene have been identified: rs7041 and rs4588. These coding single nucleotide polymorphisms (SNPs) track with ancestry (African *versus* European), determine the amino acid changes in DBP1F (rs7041-T (Asp), rs4588-C (Thr)), DBP1S (rs7041-G (Asp), rs4588-C (Thr)) and DBP2 (rs7041-T (Asp), rs4588-A (Lys)) and associate with total 25(OH)D [2]. The occurrence of DBP polymorphisms depends strongly on the ethnic background: darker pigmented African, African American, and Asian populations are more likely to carry the DBP1F variant, whereas the DBP1S form is more frequently observed in white populations [4]. In the first large genome-wide association study (GWAS) of 25(OH)D concentrations in 33 996 white individuals of European descent from 15 cohorts [5], a significant association between rs7041 and circulating 25(OH)D was demonstrated ($p=6.31\times10^{-59}$), whereas the rs4588 variant was not included in the HapMap dataset and was not part of the results. However, the latter variant can be regarded as the minor variant predicting 25(OH)D concentrations. The relationship between these GWAS associations and race was not explored in this study. A recent paper suggested that these SNPs in the *DBP* gene, specifically in the rs7041 locus, correlated with the prevalence (GT genotype: r=0.73, p=0.02; TT genotype: r=−0.62, p=0.04) and mortality (GT genotype: r=0.87, p=0.01; TT genotype: r=−0.66, p=0.04) rates of COVID-19 among all investigated populations [6]. In more detail, subjects with a TT genotype had a higher COVID-19 susceptibility in China, Japan, Nigeria and Kenya. Racial differences in the prevalence of these common genetic polymorphisms might result in an altered vitamin D metabolism, influencing acute lower respiratory infection disease severity. A high risk for vitamin D deficiency has also been demonstrated in carriers of two T alleles of the rs7041 variant in, for example, patients with COPD [7]. Although the study of Faniyi *et al.* [1] suggested that vitamin D deficiency is an independent risk factor for the development of COVID-19 seroconversion, with the biggest differences in the BAME male group, a recent, not yet peer-reviewed Mendelian randomisation

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study on vitamin D and COVID-19 susceptibility and severity in individuals of European ancestry, showed no protection of genetically increased 25(OH)D concentrations against COVID-19 susceptibility, hospitalisation, or severe disease. No evidence supports a protective role for vitamin D supplementation in COVID-19 outcomes. It should be noted that these results do not apply to individuals with a true vitamin D deficiency and that only the effect of 25(OH)D on COVID-19 in individuals of European ancestry was studied, and not in other populations [8].

Finally, it should be mentioned that a large GWAS in 79 366 European-ancestry individuals reported six significant loci involved in the genetic variation of 25(OH)D, which include, besides the *DBP* gene, the DHCR7/NADSYN1 region (DHCR7 is involved in a conversion of a 25(OH)D precursor molecule to cholesterol) and CYP2R1 and CYP24A1 genes (which encode enzymes involved in 25(OH)D metabolism). In total, common SNPs explain 7.5% (standard error 1.9%) of the variance of 25(OH)D [9]. A recent, even larger GWAS (n=417 580 Europeans) identified 143 loci related to lipid- and lipoprotein-related pathways with an influence on 25(OH)D concentration [10].

In conclusion, besides adiposity and skin pigmentation, which were taken into account in the paper of Faniyi *et al.* [1], different loci (*e.g.* the *DBP* gene) could also partly influence the low 25(OH)D concentrations in the BAME group with COVID-19.

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