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Androgen Receptor Genetic Variant Predicts COVID-19 Disease Severity: A Prospective Longitudinal Study of Hospitalized COVID-19 Male Patients

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Abbreviations:

5ARi: 5-alpha reductase inhibitors

ICU: Intensive care unit

TMPRSS2: Transmembrane protease, serine 2

AA: Androgenetic alopecia

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To the Editor, Men infected with SARS-CoV-2 are more likely to be admitted to the intensive care unit (ICU) compared to women.[1] Previously, we have reported that among hospitalized men with COVID-19, 79% presented with androgenetic alopecia (AA) compared to 31-53% that would be expected in a similar aged match population.[2] AA is known to be mediated by variations in the androgen receptor (AR) gene.[3] In addition, the only known promoter of the enzyme implicated in SARS-CoV-2 infectivity, TMPRSS2, is regulated by an androgen response element.[4] The polyglutamine repeat (CAG repeat) located in the AR gene is associated with androgen sensitivity and AA.[3] These observations led us to hypothesize that variations in the AR gene may predispose male COVID-19 patients to increased disease severity.

We conducted a prospective longitudinal study of hospitalized COVID-19 males. The subjects were categorized into two cohorts: subjects with a CAG>=22 and subjects with a CAG<22. Subjects taking androgen modifying drugs, e.g., 5ARis, were excluded. DNA was collected using ORAcollect•Dx: (DNAGenotek, Ottawa, Canada). AR CAG repeat region was PCR-amplified and 300bp paired-end sequencing was performed using a MiSeq (Illumina, San Diego, California). Reads were mapped to reference AR sequences containing 1 to 50 CAG repeats, the reference with the greatest number of mapped reads was reported as the CAG repeat count. Subjects were followed for a period of 60 days from the date of hospitalization. Primary and secondary outcomes were the rate of ICU admissions and length of hospitalization, respectively.

77 COVID-19 positive men were recruited to the study; 12 were excluded due to their use of androgen modifying drugs, leaving 65 patients enrolled in the study. 31 (48%) subjects had a CAG<22, with average age of 67.9 (+/- 12.3). The median duration of hospitalization among subjects with a CAG<22 was 25 days (95% CI: 9.000-41.6512), and 14 (45.2%) were admitted to the ICU. 34 (52%) subjects had a CAG>=22, their average age was 65.0 (+/- 12.15). Among the 34 subjects with a CAG>=22, the median duration of hospitalization was 47.5 days (95% CI: 22.9533-49.0935), and 24 (70.6%) were admitted to the ICU.

The proportion of subjects admitted to the ICU with CAG<22 was significantly lower than the proportion of subjects with CAG>=22 (Fisher's exact test p= 0.046791. Subjects with a CAG>=22 had a higher risk for ICU admissions compared to subjects with a CAG<22: OR 2.9143(95% CI: 1.0487-

8.0985) and Likelihood Ratio 1.705(95% CI: 0.985-2.951). Further, estimating 40% of hospitalized COVID-19 male patients are likely admitted to the ICU,[5] the Bayes' adjusted positive predictive value of the AR CAG score in predicting ICU admissions was 53.202% (95%CI: 39.646%-66.301%) and the negative predictive value was 71.938% (95%CI: 60.693%-80.974%).

Our data suggest that longer AR CAG score is associated with more severe COVID-19 disease. In some androgen mediated disease, short CAG has been associate with worse prognosis, e.g., in prostate cancer.[6] However, in skeletal muscle, a long CAG repeat length produces higher androgen mediated activity.[7] We believe this discrepancy can be explained by the tissue dependent expression of co-factors important for activation of the androgen response element (ARE).[8] For example, protein arginine methyltransferase 6 has been shown to be highly expressed in lung and has been shown to be a specific co-activator of the androgen receptor.[9]

The results of this study suggest that the AR CAG repeat length could potentially be used as a biomarker to identify male COVIID-19 patients at risk for ICU admissions. More importantly, identification of a biomarker associated with the androgen receptor is yet another piece of evidence supporting the important role of androgens in SARS-CoV-2 disease severity. We recognize the limitations of this small study; however, our findings, combined with previous reports implicating androgens in COVID-19 disease severity,[3-5] should encourage other groups to explore interventional studies of anti-androgens in COVID-19 patients. Currently, we are conducting a double-blinded interventional study with dutasteride (NCT04446429).

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