Using the 100,000 Genomes Project to Explore SARS-CoV-2 Infection Susceptibility in the UK Rare Disease Population

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Background

Since its emergence in December 2019, SARS-CoV-2 has had enormous impact as a global health threat. Age, gender, and the presence of co-morbidities are well established risk factors for both mortality and severe disease. Several host genetic factors have been linked to disease severity, including variants in *ACE2*, *TMPRSS2* and the *OAS* gene cluster. The role of genetic factors in relation to infection susceptibility, rather than outcome, has been less of a focus. Determining risk factors for infection susceptibility is crucial for identifying individuals at risk and allows tailoring of public health measures, such as shielding, to those who would most benefit. This project sought to explore the role of host genetic background in determining SARS-CoV-2 infection susceptibility in the patients with a diagnosed rare disease.

Methods

SARS-CoV-2 PCR test results of 2738 participants of the 100,000 Genome Project rare disease cohort were associated with genotype at 25 pre-selected loci. Associations were determined using Fisher's test using samples of participants subset by disease, as well as across the cohort as a whole. Association testing was also performed between positive tests and disease classification to identify any disease groups with significantly higher rates of infection.

Results

Four variants (rs10735079, rs1156361, rs143334143 and rs10774671) were significantly associated with SARS-CoV-2 infection among 100K rare disease cohort. Three of these are co-located within the *OAS* gene cluster and is particularly associated with infection among participants with neurodevelopmental disorders. It was also found that participants with disorders of sex development were significantly more likely to receive a positive SARS-CoV-2 test result than other participants.

Conclusion

These findings suggest that variation in *OAS* genes may influence individual susceptibility to SARS-CoV-2. As this locus has previously been associated with severe COVID-19, this suggests that molecular mechanisms determining infection susceptibility and disease severity may be shared. Further investigation of the observed increased susceptibility to SARS-CoV-2 in patients with disorders of sex development may provide clues to mechanisms underlying susceptibility in general, as well as previously observed sex bias in disease outcome.

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