Participating organisations: University of Kent (UoK), Canterbury Christ Church University (CCCU) and Dartford and Gravesham NHS Foundation Trust

Sponsor: University of Kent

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Short title: Understanding prevalence and transmission of severe COVID-19

Full title: Genetic variant analysis of individuals tested positive for SARS-CoV-2: understanding the link between BAME ethnic background and the higher risk of developing severe COVID-19.

STUDY PROTOCOL

Background

The Coronavirus Disease 2019 (COVID-19) outbreak has rapidly expanded and to date (7th June 2021) caused 174,100,828 cases and 3,745,244 deaths worldwide.

COVID-19 symptoms vary significantly between individuals, with outcomes ranging from asymptomatic infection to mild-to-moderate symptoms and severe leading to hospitalisation in intensive care units and in some cases to death. Indeed, its prevalence and numbers of infected cases, deaths, and mortality rates vary from country to country and even between regions within the same country.

To date (7th June 2021), over 4,516,892 cases and 127,840 deaths have been reported in the UK and data from the Office for National Statistics and Public Health England suggest that Black, Asian and Minority Ethnic (BAME) groups are at an increased risk of infection and death from COVID-19. In particular, when compared to the general population, individuals with Pakistani origin have a 3.29 times higher risk, those with Bangladeshi origin a 2.41 times higher risk, those with Black Caribbean origin a 2.21 times higher risk and those with Indian origin a 1.7 times higher risk. Although, this observation was made early in the pandemic and various biological (vitamin D levels) or socio-economic risk factors have been proposed, the reason why BAME groups are at higher risk compared to the general population is yet to be fully understood. Genome-Wide Association Studies suggest that genetic factors may be the key to understand the higher risk of this population to acquire a SARS-CoV-2 infection and develop severe symptoms. In support of this, several DNA sequence variations or Single Nucleotide Polymorphism (SNP) known to increase the risk of developing a range of complex diseases e.g., cardiovascular diseases, auto-immune diseases and acute respiratory distress syndrome, have been linked to the BAME groups. Thus, it is clear that the interplay of SARS-CoV-2 infection, genetic variants and presence or onset of other morbidities, needs to be further investigated in the BAME population.

Hypothesis and Aim

We hypothesise that individuals belonging to the BAME ethnic groups, already known to be at higher risk for cardiovascular disease, may carry genetic variants, which in combination with SARS-CoV-2 infection can result in severe or fatal COVID-19 symptoms. Therefore, we aim to conduct a pilot study on individuals tested positive for SARS-CoV-2 at the North Kent Pathology Service (Dartford and Gravesham NHS Foundation Trust), and investigate whether COVID-19 susceptibility and severity is linked to specific genetic variants among different ethnic groups (BAME vs other ethnic groups).

Preliminary work

We have led in the establishment of a point-of-care COVID-19 testing facility in the North Kent Pathology Service (Dartford and Gravesham NHS Foundation Trust) to support the county of Kent (South-eastern England). The testing facility has been operational since April 2020. Since June 2020, we have established a bank of SARS-CoV-2 swabs and stored over 3,000 anonymised (non-identifiable) samples from individuals who, as part of their normal care, have been tested positive for SARS-CoV-2 at the North Kent Pathology Service (Dartford and Gravesham NHS Foundation Trust). The sample collection is fully supported by the point-of-care at the North Kent Pathology Service (Dartford and Gravesham NHS Foundation Trust) providing administrative support with samples storage/processing and clinical data access. Each SARS-CoV-2 positive nasopharyngeal swab after the testing is transferred in a tube identifiable only by a unique number (not containing any personal information) and will stay anonymised from sample processing to data dissemination. Participants will be informed for the use of their samples and consent will be sought prior starting the research. HRA approval has been granted.

Participants recruitment

NHS/point-of-care staff will get in touch (firstly by phone) with the participants (tested for SARS-CoV-2 at the North Kent Pathology Service as part of their normal care) to inform them about the research project and seek consent for the use of their samples for research. Thereafter, Participant Information Sheet, Informed Consent and Questionnaire will be posted to the participants. Children and adults unable to consent are excluded from the study. Once patients' signed consent forms are obtained, we will proceed with sample processing and genetic analysis. Samples are fully anonymised (non-identifiable) and researchers will run the experiments blinded. Only clinical data relevant to the study will be considered, handled by NHS/point-of-care and University staff, stored on password protected NHS/University computers and treated with the outmost confidentiality. Data will be disposed 5 years after the end of the study, in accordance with the Human Tissue Authority Code of Practice.

Research plan 1

We have secured funding from NHS Charities (Dartford and Gravesham NHS Foundation Trust) which will allow investigation of genetic COVID-19 risk factors in a subset of the stored swabs (up to 300 swabs) from BAME individuals which will be compared to other ethnic groups.

Clinical analysis: demographic data (e.g., age, gender, ethnic origin) and relevant clinical data such as the presence of comorbidities and COVID-19 outcome will be extracted for each SARS-CoV-2 positive swab stored in the swab bank. This initial analysis will reveal the degree of correlation between patient ethnic origin, pre-existing health conditions and severity of COVID-19 within the Trust. The sample cohort will be then grouped according to ethnicity (BAME *vs* other ethnic groups) as well as underlying health conditions to seek their possible linkage with genetic variants (SNPs).

Genomic analysis: we will investigate whether certain Single Nucleotide Polymorphism (SNP), associated with COVID-19 induced respiratory failure and cardiovascular diseases, correlate with BAME ethnic origin and COVID-19 symptoms and disease severity. The genomic analysis will be performed as previously described (*R Vuono et al, Brain 2015; R Vuono et al, Movement disorders 2019*) and by using the TaqMan allelic discrimination assay according to the manufacturer's instructions.

The genetic analysis will be then correlated with NHS clinical data available for the participants to identify pre-existing co-morbidities and how this may have had an impact on COVID-19 symptoms, potential hospitalisation, and recovery.

Outcome

Our findings can assist clinicians in disease prognosis and selection of effective treatments with a tailored response to patients' needs. This is crucial in managing the new arising SARS-CoV-2 variants as well as future pandemics.