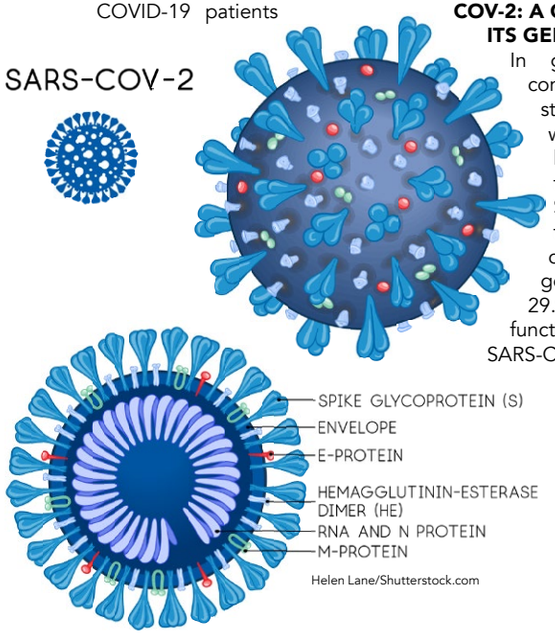
Understanding SARS-CoV-2

A closer look into its genome

A team of BARJ scientists from the Bangladesh Jute Research Institute, Dhaka, Bangladesh have conducted significant research on SARS-CoV-2, the virus responsible for causing COVID-19. In a recent research project, BARJ researchers collected samples from positive coronavirus patients and conducted a comparative study to analyse differential host responses in various SARS-CoV-2 infection systems. In another project, the research team predicted potential intermediate hosts of the COVID-19 virus that can spread this infection in the southern region of Asia.

The coronavirus pandemic has spread across the globe and killed more than three million individuals. It is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and is thought to have originated in bats and spread to humans through intermediate hosts. The number of COVID-19 patients is increasing at an alarming rate across many countries. Scientists around the world are working tirelessly to understand the mechanism of the virus and find better therapeutic interventions to control the rate of infection.



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UNDERSTANDING SARS-COV-2: A CLOSER LOOK INTO ITS GENOME

In general, coronaviruses contain RNA (single-stranded) genomes with an approximate length of 30 kb. Among the coronaviruses, SARS-CoV-2 belongs to a group of beta-coronaviruses with a genome length of around 29.9 kb. It contains 11 functional genes. Although SARS-CoV-2 shares clinical characteristics with the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) viruses, it only shares 79% and 50% genome sequence similarities with these viruses, respectively. The genomic sequence of SARS-CoV-2 is 90% identical to the bat-derived SARS-like coronavirus. There are also reports showing various key genomic differences between SARS-CoV-2 and SARS-CoV including 380 different amino acid substitutions, ORFa deletion and ORF8b elongation.

DIFFERENT TRANSCRIPTIONAL HOST RESPONSES IN COVID-19 PATIENTS

Using the latest sequencing technologies, BARJ researchers from the Bangladesh Jute Research Institute designed a study to sequence the genome of SARS-CoV-2 from Bangladeshi patients. They began with collecting nasopharyngeal (upper part of the pharynx, connects nasal cavity above the soft palate) swab samples of COVID-19 positive patients from the Chattogram region with support from the Chattogram Veterinary and Animal Sciences University. Their aim was to profile the COVID-19 patient transcriptome (the sum of all the messenger RNA's molecules expressed by the genes in an organism) from nasopharyngeal swabs and the genomic features of the virus isolated from each host. They compared different host responses in several SARS-CoV-2 infection systems.

One of a kind, this study from South Asia reports genome variations observed in the four SARS-CoV- isolates. The researchers investigate the variations in host transcriptional responses in various COVID-19 infection models and the potential consequences of these changes. The mapped reads were assembled de novo (a method for constructing genomes from a number of DNA fragments). The team applied the "Variation Identification" tool on the China National Center for Bioinformation's "2019 Novel Coronavirus Resource (2019nCoVR)" portal to identify the variations in their sequenced SARS-CoV-2 genome. They then utilised the same portal's "Variation Annotation" method to annotate the variations of the isolated SARS-CoV- isolates. The Ensembl Variant Effect Predictor (VEP) tool was applied to further characterise the impacts of the variations.

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BARJ researchers designed a study to sequence the genome of SARS-CoV-2 from Bangladeshi patients


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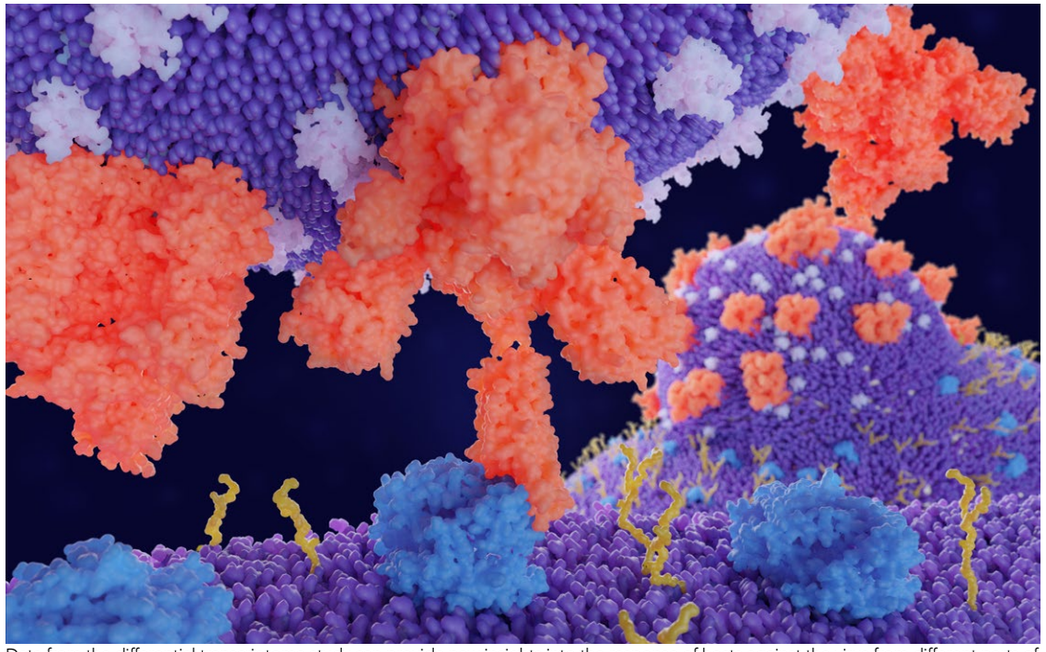
The researchers conducted a comparative study to analyse differential host responses in various SARS-CoV-2 infection systems.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is likely to have originated in bats and spread to humans through intermediate hosts.

All of the reported isolates had unique and rare missense mutations in the 3C-like protease. According to the functional enrichment analyses, innate immunity, interferon, and cytokine activation were involved in the host-induced responses. Surprisingly, these patients show no activation of apoptosis, phagosome, antigen presentation, or hypoxia (deficiency of oxygen) response. In the lungs, immune and cytokine signalling genes including *CCL4, TNFA, IL6, IL1A, CCL2, CXCL2, IFN* and CCR1 were found to be up-regulated. There was a lack of angiotensin I converting enzyme -2 (ACE2) overexpression in the lungs, although high ACE2 and low DPP4 expression were detected in nasopharyngeal cells.

IDENTIFICATION OF POTENTIAL INTERMEDIATE HOSTS - DATA FROM SOUTH ASIA

In another significant research project, BARJ team used silico (computer-based) approaches to predict the potential hosts and intermediate hosts of SARS-CoV-2. They conducted diversity analysis of ACE2 and transmembrane protease serine 2 (TRMPRSS). ACE2 acts as a cellular receptor for SARS-CoV-2, while TRMPRSS helps in



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Data from the differential transcriptome study can provide new insights into the response of hosts against the virus from different parts of the respiratory tracts.

spike protein priming. Phylogenetic (evolutionary development) trees based on the amino acid (aa) sequences of ACE2 and TMPRSS2 were created for this purpose. Human ACE2 was found to be clustered with rhesus macaques but separated from mouse and rat ACE2 in both trees. In these trees, members of the Bovidae family, such as cows, buffaloes, goats, and, sheep formed a cluster, while all the bird species clustered with chicken.

In this study, they also stimulate the structure of SARS-CoV-2S RBD (receptor-binding domain of SARS-CoV-2 spike protein) with ACE2s. It was performed to investigate their binding affinity and identify potential intermediate animal hosts responsible for spreading coronaviruses to human in South Asia. Based on the recently solved crystal structure of the SARS-CoV-2S RBD in complex with human ACE2, they identify 20 possible aa residues of ACE2 that are essential in interacting with SARS-CoV-2. The utilisation potential of SARS-CoV-2S RBD was predicted based on the sum of 20 individual scores to produce a cumulative final score. Rhesus macaque was the only species, with 100% similarity to human ACE2, to be as susceptible to SARS-CoV-2 as humans. Common in the household farming system of South Asia, species like a cow, buffalo, goat and sheep from family Bovidae received a high score of 80. Rat, mouse and bird species received a score of less than 50. Through this analysis, the research team have identified cow, buffalo, goat and sheep as animals that can be potentially infected by this virus. ACE2 protein complex and SARS-CoV-2S RBD interaction interfaces highlight pangolin as a possible intermediate host in SARS-CoV-2.

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FUTURE PERSPECTIVE

Data from the differential transcriptome study can provide new insights into the response of hosts against the virus from different parts of the respiratory tracts. Despite the fact that this research only includes a small number of cases, the findings can aid in the development of future studies to elucidate the different host responses to viral pathogenesis. With further research, more data can be incorporated and enrich the quest for effective therapeutics. The findings of the potential intermediate host study can provide a valuable resource for identifying possible hosts for SARS-CoV-2 in South Asia. With proper management of potential and intermediate hosts, the risk of a COVID-19 outbreak in the future can be reduced.

Research Objectives

The COVID-19 was first described in Wuhan in December 2019 and since March 2020, it has spread throughout Bangladesh by community transmission. Little is known about the host genetic contribution to the observed inter-individual phenotypic variability. By sequencing the entire SARS-CoV-2 genome, we can pinpoint the genetic changes that occur in the virus as it spreads through the population. This can help us design effective approaches to control and prevent COVID-19 infections.

References

Ahmed, R., Hasan, R., Siddiki, A. Z., & Islam, M. S. (2021). Host range projection of SARS-CoV-2: South Asia perspective. *Infection, Genetics and Evolution, 87*, 104670.

Islam, A. B. M. M. K., Khan, M. A. A. K., Ahmed, R., Hossain, M. S., Kabir, S. M. T., Islam, M. S., & Siddiki, A. Z. (2021). Transcriptome of nasopharyngeal samples from COVID-19 patients and a comparative analysis with other SARS-CoV-2 infection models reveal disparate host responses against SARS-CoV-2. *Journal of Translational Medicine*, 19(1), 1-25.

Hoque, M. N., Rahman, M. S., Ahmed, R., Hossain, M. S., Islam, M. S., Islam, T., Hossain, M. A., & Siddiki, A. Z. (2021). Diversity and Genomic Determinants of the Microbiomes Associated with COVID-19 and Non-COVID Respiratory Diseases. *Gene Reports*, 23 (2021) 101200.

Personal Response

Do you have any plans to utilise data from your own studies and develop effective therapeutic strategies to fight COVID-19, given that many countries around the world are experiencing a second wave?

" At the time we started this work there was no available genome sequence of SARS-CoV-2 from Bangladeshi isolates. This SARS-CoV-2 genome sequence provides the research community an opportunity for diversity analysis and molecular characterisation of SARS-CoV-2 from Bangladeshi patients. Our goal is to support the health and medicine sector of Bangladesh, who conducts research to develop effective therapeutic strategies to fight COVID-19. Although our centre largely focuses on research into the jute genome and the improvement of jute varieties, we are ready to provide any type of support to the research effort associated with COVID-19 for the betterment of mankind. "

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