



GEN PHILIC

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Department of Biotechnology

Fergusson College (Autonomous), Pune.

COVID-19 | Updates | SARS-CoV-2



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Have we met this family before?

Scientists have analysed the nucleotide sequence homology of SARS-CoV-2 with the viruses related to it, for example, SARS-CoV (79.5% homology) and MERS-CoV (50% homology); this gives an idea as to the kind of drugs (already manufactured) that may work against SARS-CoV-2.

Being large doesn't make them slow...

Coronaviruses possess the largest genome (26.4 - 31.7 kb) among all known RNA viruses.

D614G : The Mutation which helped SARS-CoV-2 infect more

A change in the amino acid sequence of the spike protein has allowed the virus to bind easily to the ACE-2 receptors. The mutation switches the original 614th amino acid, aspartic acid (D) to the new variant, glycine (G).

More on this in 'The core: Genotype'



What exactly are you, SARS-CoV-2?

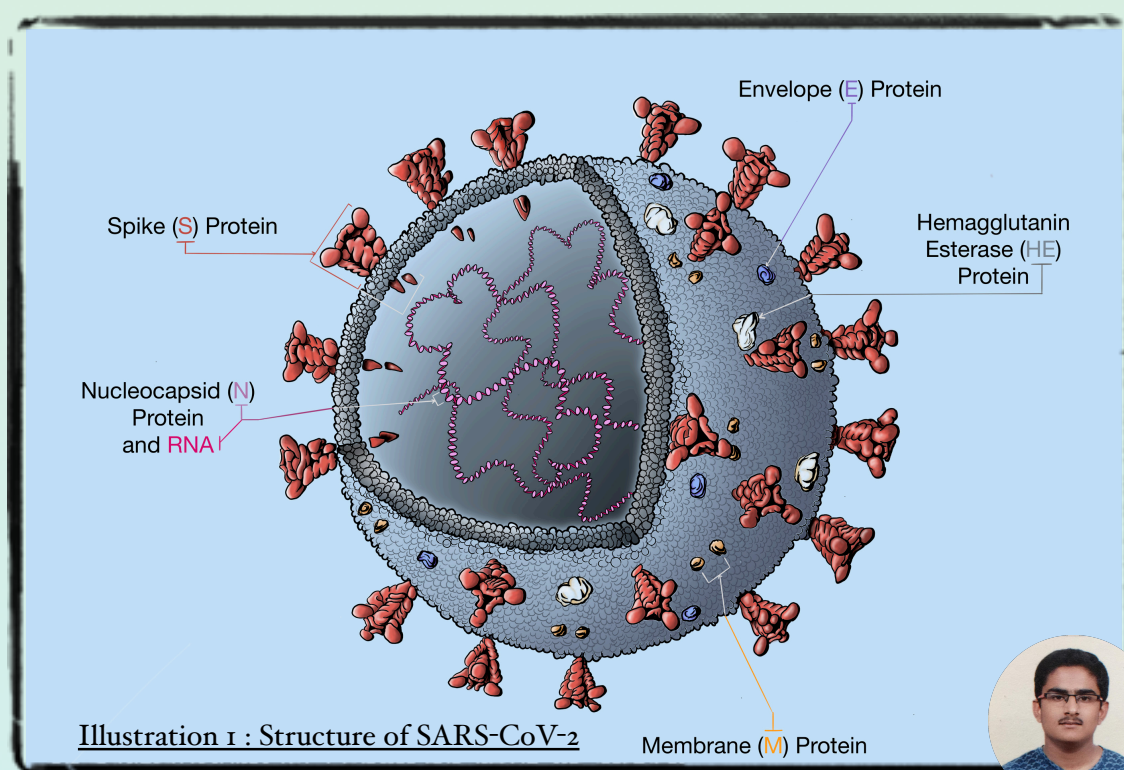


Illustration 1 : Structure of SARS-CoV-2



Illustration: Hrishikesh Hardikar.
S. Y. BSc. Biotechnology

Classification and phenotype (observable characteristics)

What if I told you there's an entire family of viruses like the Corona virus out there? No, I am not hinting at another pandemic, don't worry. The Covid-19 virus belongs to a family of viruses, *Coronaviridae* and has now been named **SARS-CoV-2**. David Baltimore has provided a method of classifying viruses based on how they replicate their genome according to which this virus belongs to class IV of positive sense, single stranded RNA viruses, enveloped in a helical nucleocapsid (N protein), a protective coat.

Upon entering the host cell, the virus releases its positive sensed RNA into the cytosol. It's similarity to the normal mRNA produced by the host helps it immediately translate into viral proteins using the host ribosomes. Some of these proteins form replication complexes to keep the cycle of producing new viral RNA going. This complex includes sub-genomic RNAs responsible for synthesis of structural proteins (S, E and M) as well as full-length transcripts to be incorporated in the genome of the new virions. The structural proteins move along the secretory pathway into The endoplasmic reticulum-Golgi intermediate compartment and encapsulated in the N protein bud off into the golgi lumen. The exocytotic vesicles of the golgi fuse with the plasma membrane and release the mature virions to infect other cells. That's how the virus increases in number, lives happily in your body while causing nothing but havoc.



By Aarjvi Jain.
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Mutations (another set) in SARS-CoV-2 over Geographical areas:-

- (I) There are 3 distinct variants of SARS-CoV-2, consisting of clusters of closely related lineages, which are labelled A, B and C.
- (II) Virus 'A' is the one most closely related to the virus found in both bats and pangolins and can be described as 'the root of the outbreak'.
- (III) Mutated versions of 'A' were seen in Americans reported to live in Wuhan, and large number of A type viruses were found in patients from US and Australia.
- (IV) Type 'B' is derived from 'A', separated by 2 mutations, then 'C' is in turn "daughter" of 'B'.
- (V) Wuhan's major virus type B, was prevalent in patients from across East Asia but the variant didn't travel much beyond the region without further mutations.
- (VI) The 'C' variant, is the major European type, found in early patients in France, Italy, Sweden and England. It is absent in samples of mainland China, but seen in Singapore, Hong Kong and South Korea.

Please pay special attention to your health :

- ❖ Senior Citizens
- ❖ Diabetic and overweight individuals.
- ❖ Heart patients; having hypertension
- ❖ Those suffering from immune diseases or those who have had an organ transplant.
- ❖ Those working in close contact with others.

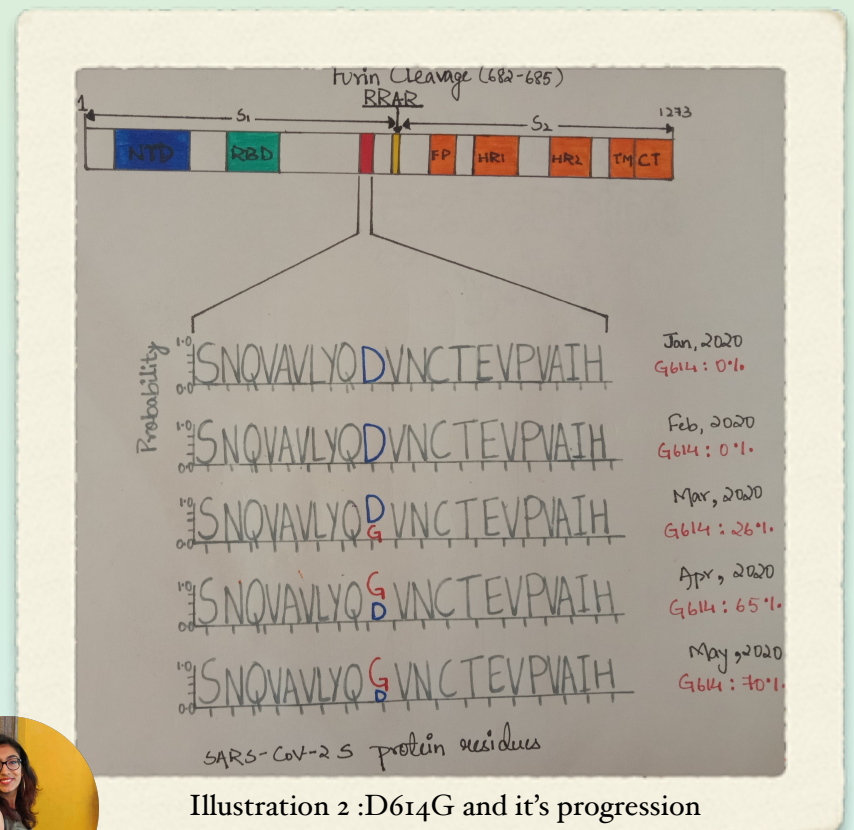
The core : Genotype

Every time a virus infiltrates its host cell, small copying errors occur during the replication of its genetic material. Each of these errors induce changes in the genomic sequence, in short, the virus mutates. It has been observed, that RNA viruses show a higher rate of mutation as compared to DNA viruses. Till now, more than 200 variants/mutants of SARS-CoV-2 have been discovered, likely due to the imperfect replication of its genome.

Experiments conducted during the early stages of the pandemic showed that the first ever prevalent gene mutation found in this virus was D614G mutation (has a change in the amino acid sequence of the spike protein).

Statistics suggest that the spread of the G variant is 1.22 times faster than the D variant, the original variant found in the infected patients of Wuhan, China.

Illustration : Divyashi Motwani
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Lab experiments were conducted by scientists in the Duke University and the La Jolla Institute of Immunology in California. They inserted the G mutation and D mutations into pseudoviruses, which are viruses engineered to display the surface proteins of other viruses.

The viral loads found in the viruses having G variations of the spike protein were 2.6 to 9.3 times larger than from those having the D variations of the spike protein.

These results coincided with the statistics that convey, the G variant represented 67% of global samples taken in March, and 78% of those taken between April 1 and May 18 (during this time, the locus of the outbreaks shifted away from China to Europe and the United States).

With these studies also comes a good news. There is no evidence so far which may suggest that the G variant increases the severity of the disease as compared to any other variant, nor does the mutation appear likely to affect the process of vaccine development, researchers agree.

A popular myth that needs to be eradicated is that the mutations in a virus are always dangerous to its host. Some mutations can also weaken the virus to a large extent. They can lead to a virus becoming so weak that it gradually disappears completely as was the case with SARS-CoV (2002-2003) outbreak.

The existence of these many variants explains why a virus may trigger waves of infection of varying severity in different regions of the world and why infections progress differently in different populations or individuals.

So the question remains, 'Why is the study of these variants important for the development of a vaccine?'.

This is because, the antibodies produced by the human body or the drugs/vaccines developed in a laboratory are designed to attack certain regions of the virus. When the virus mutates, these substances become less effective towards this new version. As such, developing a conclusive drug becomes difficult.

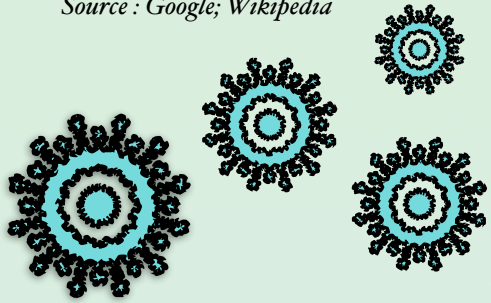
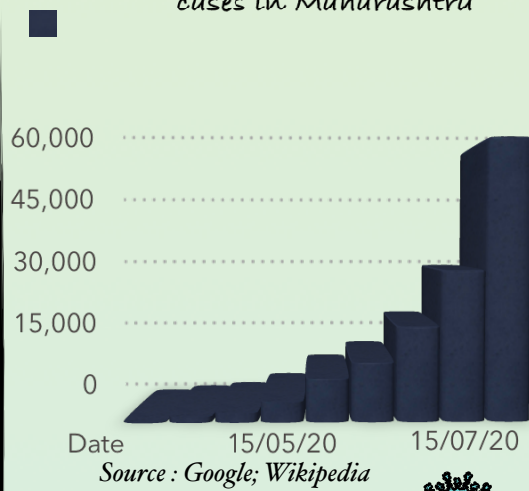
A strategy to combat this is to develop a vaccine which targets multiple regions/processes of the virus and focuses on the properties less likely to mutate i.e the invariant parts or the conserved regions of the genome.

When we focus on the human part of the virus-human dynamic, it has been observed that some variations in the ACE-2 protein might make individuals more or less susceptible to the virus. ACE-2 receptors are the proteins that act as the entry point of SARS-CoV-2 into the host cells.

One of the reasons SARS-CoV-2 is highly infectious is because it can bind to the ACE-2 receptor with higher affinity as compared to SARS-CoV (2003) which was less contagious and had a lesser influence.

Based on the analysis of a study in which the researchers gathered the data regarding the ACE-2 variants from

Increase in the number of cases in Maharashtra



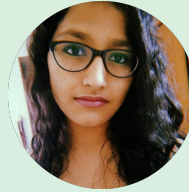
over 300,000 individuals from across the globe, it was observed that some variants bind to the virus less tightly and hence make the individuals less susceptible. It has also been found that genetic polymorphisms exist in the *ACE-2* gene; this suggests that allelic variants of the *ACE-2* may influence the protein's binding with the virus.

Some variations in the *ACE-2* protein gene can decide upto which extent the virus will bind to *ACE-2* – strongly or weakly.

Vaccines take a long time to be developed and approved, hence, majority of experiments for now are being focused on the development of new antivirals and analysing the effect of the already developed antivirals on COVID-19.

As of 8 May 2020, two medications have received emergency use authorisation (EUA) from the Food and Drug Administration (FDA): the antiviral remdesivir and a drug used to sedate people on a ventilator.

These drugs along with many others are still undergoing clinical trials.



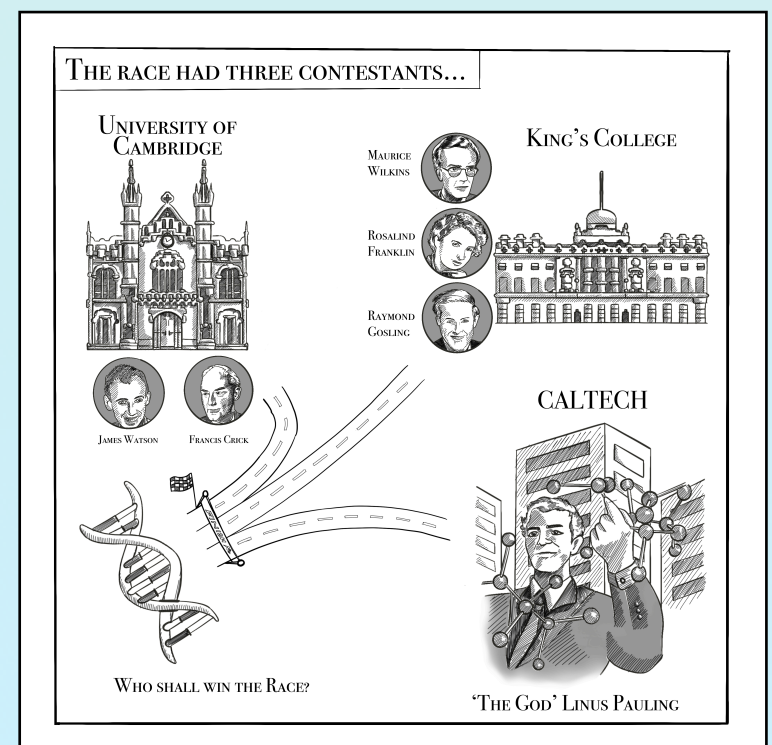
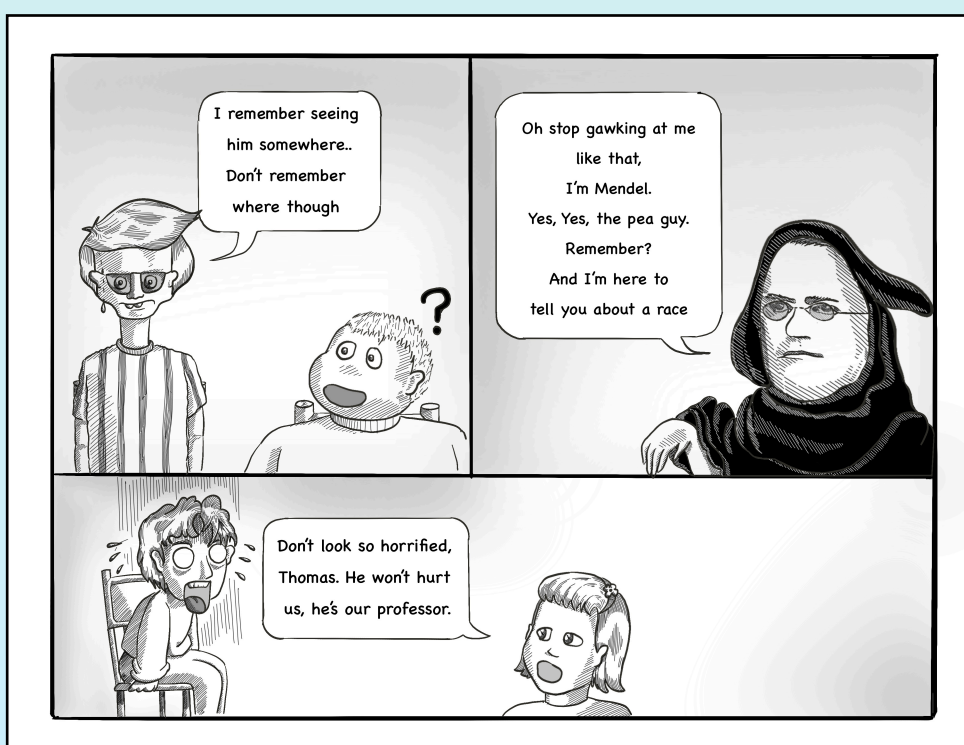
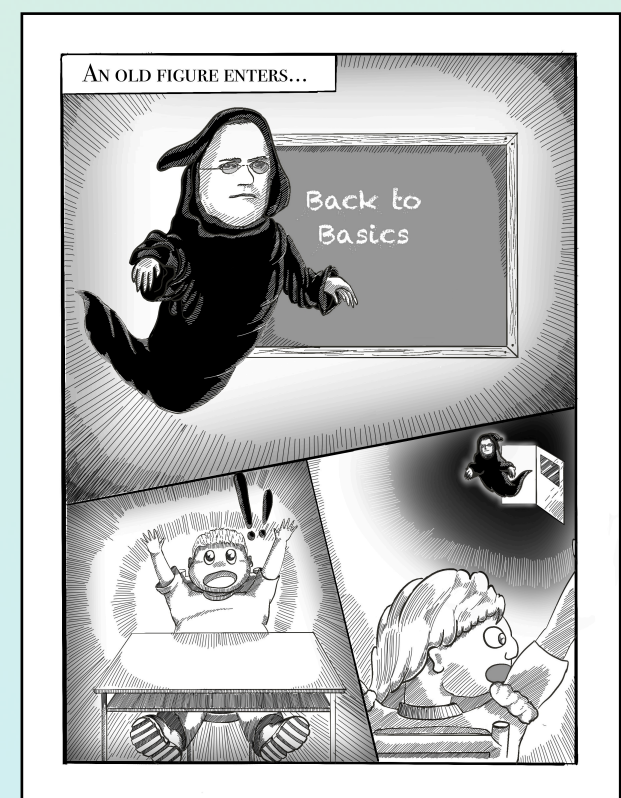
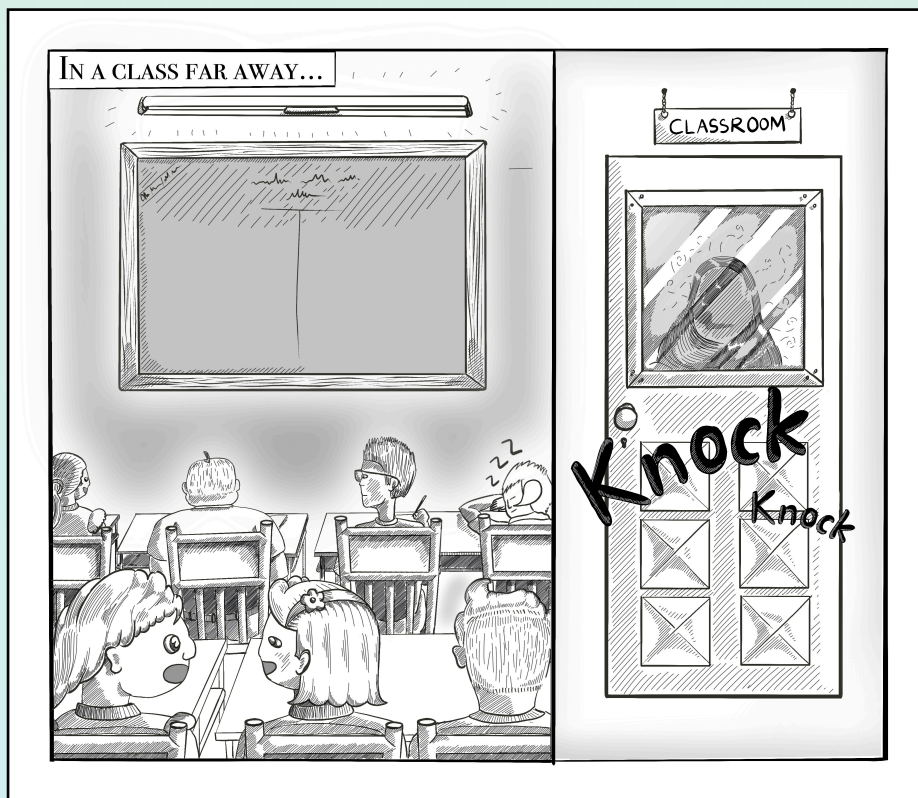
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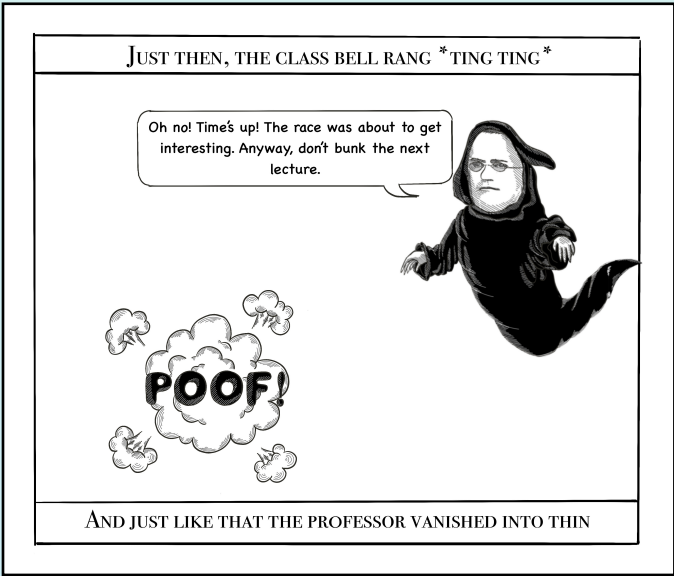
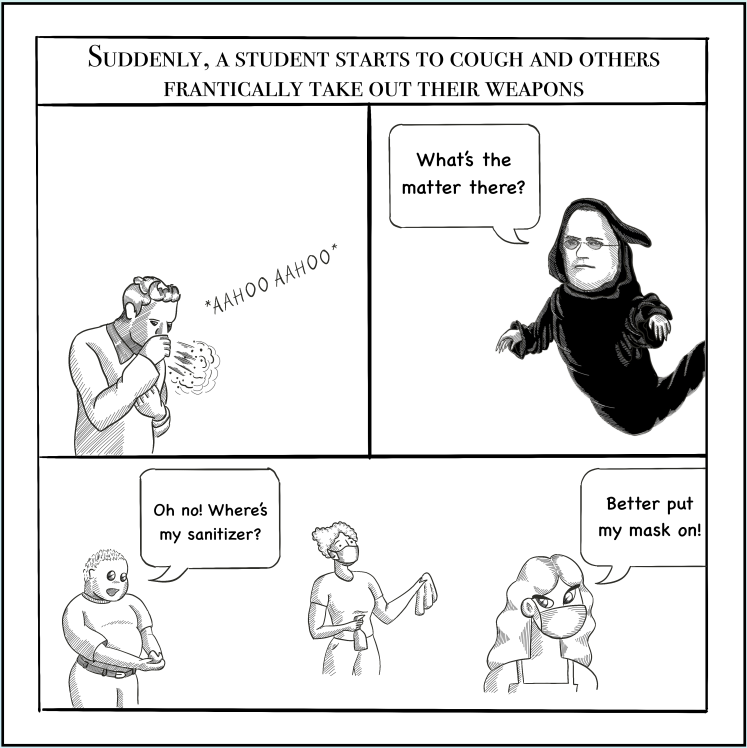
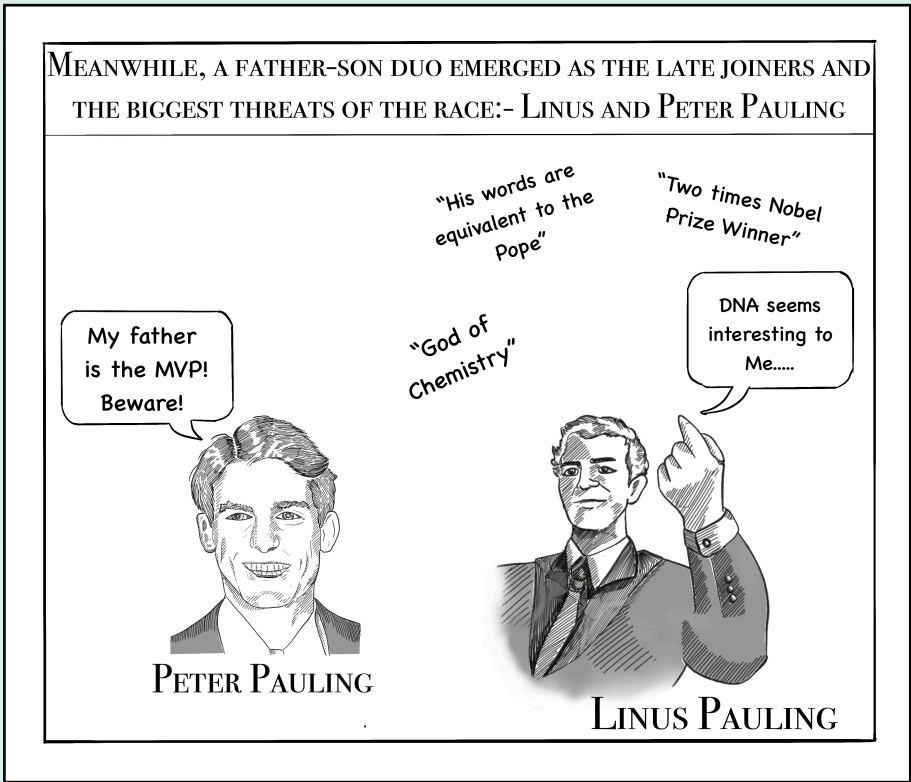
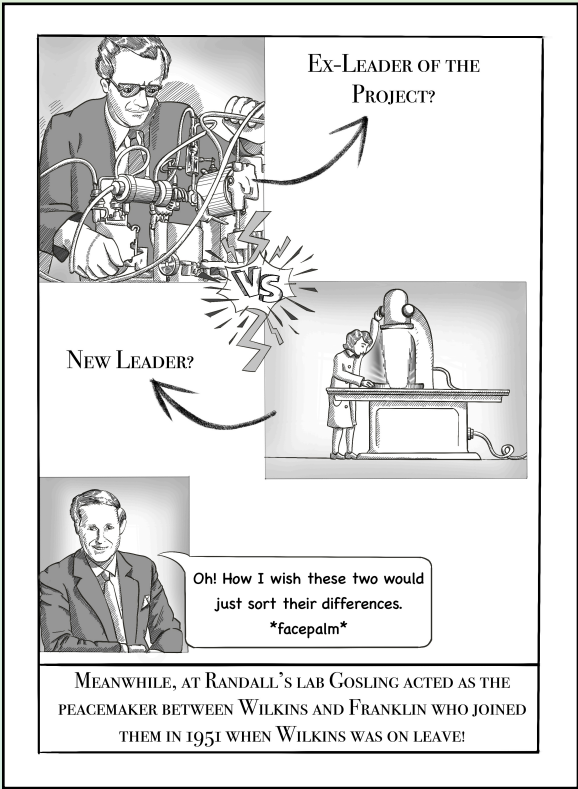
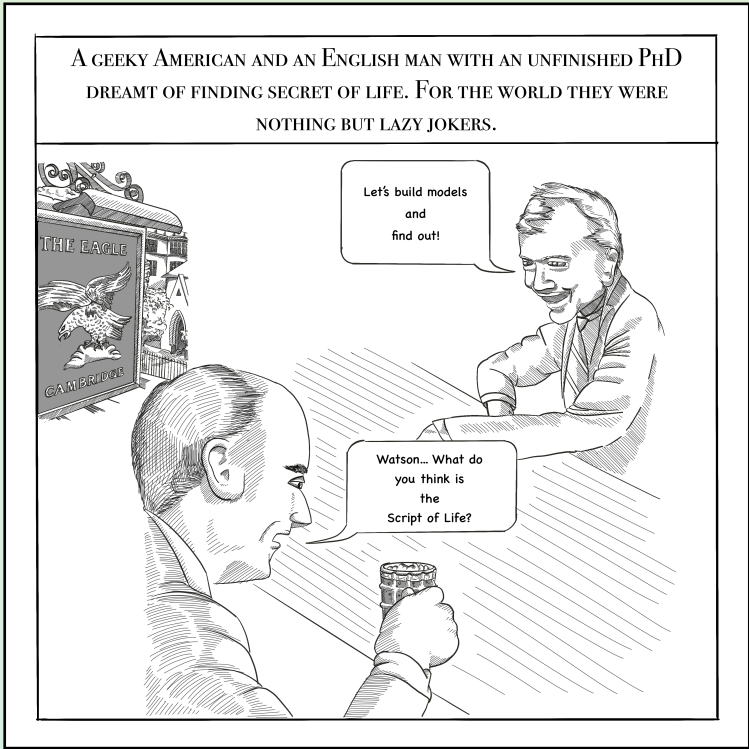


And Aqsareha Mujawar
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Back to the Basics with Friendly Ghost Grandpa Mendel

You know the legendary Gregor Mendel. You might not know the legends in the race to find secret of life! Come, discover the story with Mendel himself, and see where the journey takes you! (Note : Read from left to right)





Author : Aarjvi Jain
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Illustrator : Hrishikesh Hardikar
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Blood, Genes and COVID-19

As COVID-19 continues to infect more people across the globe, scientists have determined certain risk factors tied to more severe case of the disease which may include increased age, comorbidities like diabetes, heart diseases, cancer and lifelong experiences of systemic racism. More recently, some connections to certain genes are emerging which may explain why certain people experience more severe form of the disease and why some only develop very mild symptoms.

To study how people's genes can influence how their bodies react to the SARS CoV-2 virus, scientists have used a technique called genome-wide association study (GWAS) and collected samples from patients hospitalised with COVID-19 infections and healthy people. They have identified variants in two regions- the locus that encodes blood type and a multigene cluster on chromosome 3.

A GWAS analysis studies the genome of people with COVID-19 and compare those who didn't get very sick to those who experience severe symptoms. The findings of this study would indicate how people vary in their susceptibility to infections and how variation in the human genome plays a role in that susceptibility.

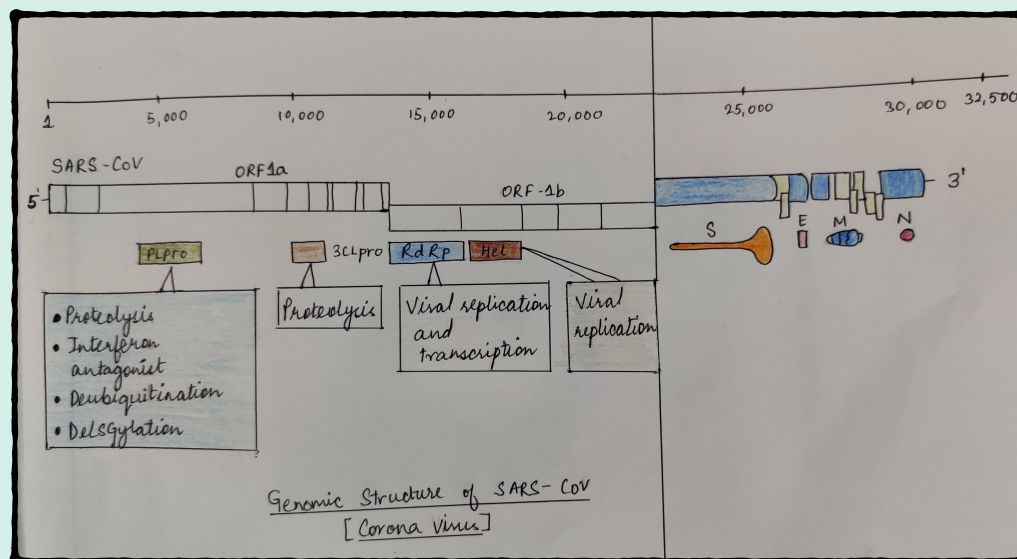


Illustration 4 : Genomic structure of SARS-CoV-2

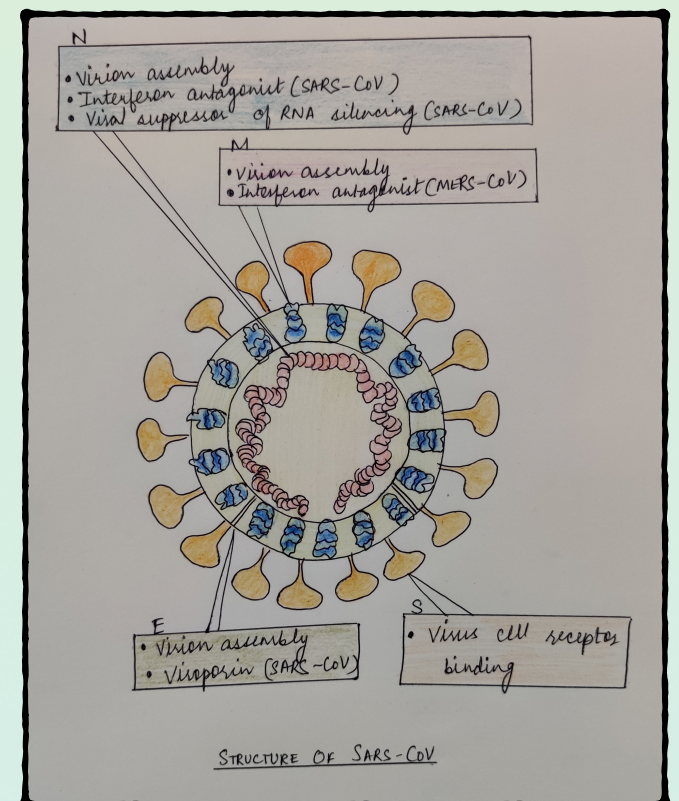


Illustration 3 : Structure of SARS-CoV-2



Illustration : Roshni Rout
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One region, as mentioned is the locus that encodes blood type and scientists found that people with blood type A are at a higher risk of respiratory failure while blood group O seems to be protective.

The other region shows up on human chromosome 3 and contains several genes of interest. One of them is SLC6A20 which encodes a transporter protein that interacts with ACE2, the main receptor that helps SARS CoV-2 get inside human cells. Two other genes called the C-X-C chemokine receptor and the CC chemokine receptor in this cluster encode immune system related chemokine receptors which helps in T-cell differentiation and recruitment during viral infections. Hence, it is concluded that the chromosome locus 3 may be involved in COVID-19 susceptibility with a possible enrichment in patients who develop severe forms of the disease.

Scientists have also recently found a genetic mutation that might render some people more vulnerable to COVID-19. The TLR genes produce protein receptors on surface of cells and help in the recognition of pathogens like viruses and bacteria. TLR7 triggers production of immune system cells type I and type II interferons which are essential in defence against viral infections. Some people might have alterations in the TLR7 gene which may result in very few or none of these receptor proteins being produced. Hence, the SARS CoV-2 virus enters the cell and starts replicating but the immune system doesn't get activated and defence against the virus is hardly present which could explain the reason for the severity of the disease.

Thus, knowledge about genes involved in the serious disease outcomes may help in identifying and developing therapeutic drugs against the disease and for fighting the pandemic.



By Sifa Lalani
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And Pragyananda Choudhury
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A Blast from the Past

DNA linked to Covid-19 inherited from Neanderthal DNA with respect to chromosome 3

Modern humans and Neanderthals shared a common ancestor roughly 500,000 years ago. Then their populations split and evolved in parallel. Due to interbreeding, they exchanged DNA, and thus we possess some genetic sequences which come from Neanderthal ancestry. Some of the genes that differ between humans and Neanderthals and play a part in some diseases are:

- 1) RPTN gene which causes diseases like restrictive Dermopathy, Lethal and Autosomal Recessive Congenital Ichthyosis.
- 2) SPAG17; a gene that causes Non-Syndromic Male Infertility.
- 3) CAN15; no disease has been associated with this genes as of now.
- 4) TTF1; causes Borjeson-forssman-lehmann syndrome, hypothyroidism, severe chronic interstitial lung disease and is a critical determinant of lung epithelium-specific gene expression.
- 5) PCD16 causes abnormal ciliary function, leading to respiratory distress, chronic sinopulmonary disease which includes sinusitis, bronchiectasis.

The variant of microcephalin was common outside Africa, but the only difference this variant made was that it was responsible for rapid brain growth in humans.

Neanderthal variants affected the risk of several diseases as time passed. A recent study identified a gene cluster passed down from Neanderthals, 60,000 years ago on chromosome 3 that was the risk factor for respiratory failure in SARS-CoV-2 infected patients. An early study found two genomic regions associated with severe COVID-19 symptoms:

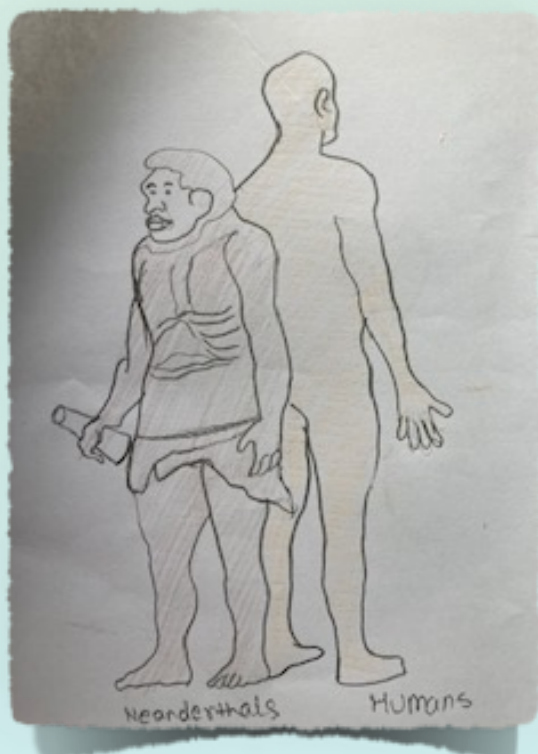


Illustration 5 : Human and Neanderthal

1. A region on chromosome 3 containing six genes.
2. A region on the chromosome 9 that determines the ABO blood group.

A recent study from the COVID-19 Host Genetics Initiative found out that the region on chromosome 3 is the only region which is associated with COVID-19 at the genomic level.

Researchers found out that many patients with severe COVID-19 symptoms had variants on chromosome 3. Some of these genes encode the proteins, called chemokines (messenger molecules) which interact with the immune system and give immune cells information about the pathogens. They attract immune cells to tissues and direct them to destroy the infected cells. The alteration is related to the increased activity of another gene that encodes a protein called angiotensin-converting enzyme 2, or ACE2.

Studies also show that 1.5-2.1% of the genetic material in non-African populations is inherited from Neanderthals.

The study of DNA linked to covid-19 has been carried out by a pair of Swedish geneticists Svante Paabo and Hugo Zeberg. The study showed that prevalence of Covid-19 is more in people who belong to South Asia as compared to Europe; this fact is attributed to the presence of the risk variant on chromosome 3 in these populations, 30% in South Asians and 8% in Europeans. This is said to be due

to the interbreeding effect that took place between humans and Neanderthals around 60,000 years ago.

A fact to be noted is that 63% of the population of Bangladeshi people carries a minimum of one copy of the risk variant present on chromosome 3. Later on it was found that this particular gene set is present only in 4% of American population and in frequencies even lower than that in East Asian populations.

To summarise the data, we can say that the highest frequency occurs in Bangladesh, where more than half the population (63%) carries at least one copy of the Neanderthal risk variant and 13% are homozygous for the variant. The Neanderthal variant may thus be a substantial contributor to COVID-19 risk in certain populations.

Currently, it is not known what feature in the Neanderthal-derived region confers risk for severe COVID-19 symptoms.



Illustration and article by : Akanksha Mahajan
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Woman Up!

Why Is COVID-19 Affecting Men More Severely Than Women?

The World Health Organization reported that 63% of the deaths among COVID-19 patients in Europe were men. According to Chinese researchers, 70% of those who died of COVID-19 were men. While in New York, rate of death in men is twice of that of women.

Looking at these global trends, one question comes to mind. “Why are men more prone to severe symptoms and death due to the virus compared to women?”

The answers range from biology to behaviour.

The Biology:

European Heart Journal reports that men have higher concentrations of Angiotensin Converting Enzyme (ACE2) in their blood.

It is to be noted that the entry of SARS CoV-2 into cells is largely facilitated by ACE2 receptors, to which it binds in a lock and key manner using the spike proteins present on its surface, thereby allowing it to infiltrate the cell and progress with its pathogenic cycle.

ACE2 is a protein found on the cell surface of many cell types. It is an enzyme that generates small proteins by lysing the larger protein, Angiotensin II - that goes on to regulate functions of the cell.

In the lungs, ACE2 is abundant in type 2 pneumocytes, an important cell type present in alveoli. ACE2 is a vital element in the Renin-Angiotensin-Aldosterone Pathway. It helps regulate the activities of Angiotensin 2 (ANG 2) that increases blood pressure and inflammation, increasing damage to blood vessel linings and causing tissue injury. When SARS CoV-2 binds to ACE2, regulation of ANG 2 is inhibited causing tissue damage to the lungs and the heart.

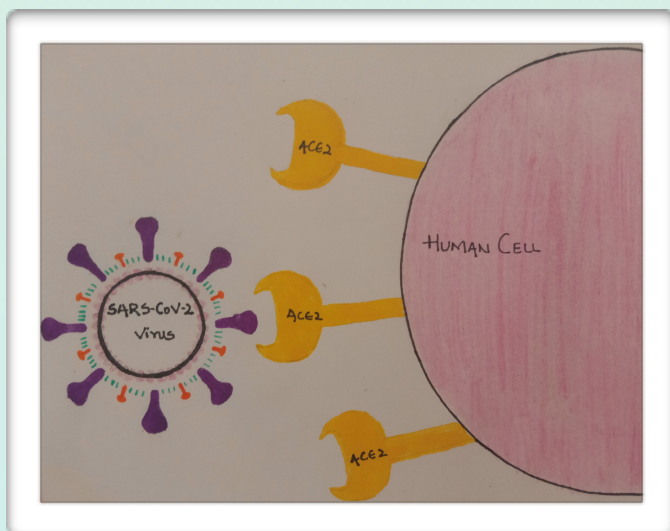


Illustration 6 : Interaction between ACE-2 receptor and SARS-CoV-2



Illustration : Divyashi Motwani
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A well established theory suggests that having an extra X chromosome results in women having stronger immune systems as most genes present on it are associated with immune response.

The reason can also be attributed to androgens, the sex hormones. In a mouse experiment, the scientists infected both male and female mice with SARS and found out that males are more susceptible as compared to female. When the ovaries of female mice were removed or their oestrogen receptors were blocked, the death rate in females increased considerably. Androgens control TMPRSS2 (an enzyme that in humans is encoded by the TMPRSS2 gene) in the lung - ground zero for SARS-CoV-2 infection - as they do in the prostate cancers.

The Lifestyle and Behaviour:

Behaviour impacting lung health, such as smoking puts men at a greater risk. Data also shows, men are more engaged in outdoor activities exposing them, which puts them more at the risk of the infection or another health issue. A study conducted in Europe shows evidence that women have a more responsible attitude in the face of the pandemic, practicing face masking and hands washing where as men are more likely to attend gatherings, events, etc.

Though men might be more susceptible to the virus and its menace, we are together in this fight and need to make sure that we follow all precautions necessary for ourselves and the community.



By Anam Namazi
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What exactly are you SARS-CoV-2?

Classification and Phenotype

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The core : Genotype

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