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EVOLUTION OF IMMUNE MECHANISMS CAN SHAPE GENETIC RISK OF MENTAL ILLNESS

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Natural selection: The researchers analysed whole exome data from 80 individuals and identified 74 genes that were positively selected. | Photo Credit: wildpixel

Evolution is a process of natural selection in which traits that improve the fitness of the organism to survive the challenges posed by its surrounding environment. However, genes have multiple effects: The very same genes that are responsible for improving an aspect of the fitness of the organism may have other contributions too, such as increasing the risk for a non-communicable disease. A paper published recently in *Scientific Reports* shows that this may be the case also with some severe mental illnesses, like schizophrenia and bipolar disorder.

The study examined 80 individuals from 80 separate families from southern India, which each had several members affected by severe mental illness. Each of these 80 individuals had at least two first-degree relatives who had a major psychiatric disorder, such as schizophrenia, bipolar disorder, obsessive compulsive disorder, dementia or substance use disorder.

Researchers from NIMHANS, Bengaluru; Institute of Genomics, Tartu, Estonia and ADBS Consortium, analysed the whole exome data from these 80 individuals and identified 74 genes that were positively selected. “Our genetic material or DNA consists of 3 billion [letters] or bases. Of this, only a small portion codes for the proteins that make up our cells,” says Meera Purushottam, from the Department of Psychiatry, NIMHANS, and a corresponding author of the paper, in an email to *The Hindu.*

Sequencing the exome means sequencing this, relatively small, portion of the genome, which codes for proteins. Under the premise that differences in the frequency of genetic variants between populations have arisen through natural selection, the researchers compared the exomes of these 80 individuals from families in southern India with multiple members having psychiatric disorders with a second, related population (random members from southern India) and a third set from an African population (which is the ‘parent’ population). This comparison revealed the genes that have been positively selected for in the 80 individuals. “So, these 74 genes that we have identified are different in more than one way in our patients and their families, compared to what we see in the population at large in this part of the world,” says Dr Purushottam.

As to the functionality of the genes, the study revealed that many of the 74 were involved in helping the body fight off diseases. “They are needed to process foreign antigens so our immune cells can recognize them as foreign, and are involved in aberrations like graft versus host disease and autoimmune thyroid disease. Many are known for having potential roles in cancer, liver disease and diabetes,” says Mayukh Mondal of Institute of Genomics, University of Tartu, Estonia, who is a corresponding author of the paper. The genes also have another side to them.

As Dr. Mondal explains, “Importantly, about 20 of them were previously associated with elevated risk for schizophrenia, Parkinson disease, Alzheimer’s Disease and cognitive abilities or intelligence. So, there is a suggestion that the risk of all these may be related at some level.”

There is also the question of the effects of ancient DNA. It is an established fact that there has

been intermingling of Homo sapiens with Neanderthals and Denisovans, hence each of us carries 2%-3% of DNA from this mixing in our genome.

The group also investigated whether any of the 74 positively selected genes contained such archaic DNA. They found only one gene that contained a sequence of Neanderthal DNA, but that sequence was itself not positively selected for. “Persistence of Neanderthal genes has been linked to risk of disease, as well as persistence of traits and body structure etc. We detected the usual amount of Neanderthal DNA in all the samples, it did not differ between the samples,” says Dr. Purushottam.

Thus, the study concludes that families with several members affected by severe mental illness can be used to detect signatures of evolution. Also, since immune-related genes show a significant positive selection in these families, the study underlines the contribution of immune mechanisms and infection susceptibility to the genetics of severe mental illness.

Dr. Sanjeev Jain of Department of Psychiatry at NIMHANS, who was one of those who designed the study, says that the risks of mental illness may be incorporated and integrated into our genome. “So we should never think of these [effects] as being different. How these widespread changes increase the risk of mental illnesses is a deep biological issue, and needs to be researched across populations. This will help reduce the stigma of mental illness, if we can reassure everyone that this is a problem that needs to be solved, rather than a burden that must be borne.”

He also adds that new treatments may emerge only after this understanding. “Mental illness cannot, and perhaps should not, be ‘eradicated’ or ‘defeated’ but managed with compassion and dignity, and an understanding that is biological as much as it is psychological,” he says.