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Neurobiology

Genes that influence handedness alter brain architecture

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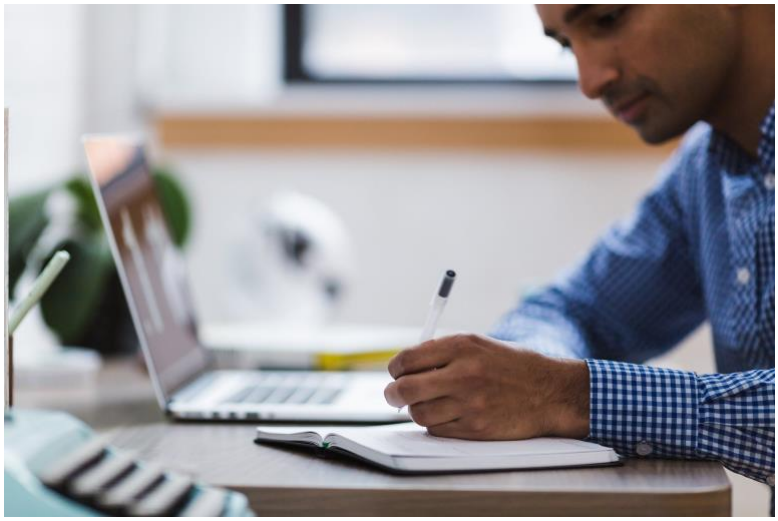
ABSTRACT

By comparing the genetic sequence of right-handers versus left-handers, we have uncovered regions in the genome that are linked to an increased chance of being left-handed. These genetic variations alter the white matter tracts that link regions of the brain related to language, and the same regions in the right and left brain hemispheres of left-handers communicate in a more coordinated way.



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For at least 10,000 years, approximately 90% of humans have preferred using the right hand over the left. The question of *why* about one in ten people are left-handed has fascinated scientists for centuries, but no clear answer has yet emerged.

We already knew that genetic factors have a partial role in determining handedness. Studies of twins have estimated that 25% of the variation in handedness can be due to genes. However, which areas of the genome are linked to handedness were not established in the general population.

To investigate this further, we harnessed the size and scale of a resource called UK Biobank, a population study of about half a million adults. We compared the genetic sequences of tens of thousands of left-handers against hundreds of thousands of right-handers to discover regions in the genome where these two groups differ (on average). We uncovered four such regions containing genetic variants associated with left-handedness.

We found that three out of four of these regions contain genes that are involved in producing proteins called microtubules. Microtubules are part of the scaffolding inside cells, called the cytoskeleton, which guides the construction and functioning of the cells in the body. In the brain, the white matter tracts – fibres that connect different areas of the brain – are made of cytoskeleton. The natural question we therefore asked was whether

the genetic variants associated with left-handedness are related to differences in the architecture of the brain.

So we looked at brain scans in a subset of UK Biobank participants to see if there were any correlations between the left-handedness associated genetic variants and brain imaging measures. We found that one of the genetic variants associated with left-handedness is correlated with differences in brain organisation, specifically in the white matter tracts that joins language-related regions of the brain.

The plot thickens further. When we looked directly for differences in the brain between left- and right-handed people, we found that the left and right sides of the brain communicate in a more coordinated way in the left-handers. Strikingly, this effect was seen in the brain regions dedicated to language that are connected by the white matter tracts associated with left-handedness. Together, these findings point to an intimate relationship between human handedness and language. They also raise the intriguing possibility that left-handers might have an advantage when it comes to performing verbal tasks.

Given that the left-handedness associated genetic variants manifest as differences in the brain, we also looked to see if there was any overlap between the "genetic structure" of left-handedness and a spectrum of neurological and psychiatric diseases. We found significant genetic overlap between our study of handedness and previous studies looking into the genetics of schizophrenia and Parkinson's disease. The genetic regions involved in left-handedness are associated with a very slightly lower chance of having Parkinson's disease, but a very slightly higher chance of having schizophrenia. This agrees with the well-established observation there are somewhat more left-handers amongst people with schizophrenia than in the general population.

It is important to stress that these links only correspond to a minimal difference in the actual number of people with these diseases, and do not show cause-and-effect. Nevertheless, there is a strong implication that these diseases, along with handedness, are the product of fundamental differences in brain development, some of which is driven by genes. Studying these genetic links could help to improve understanding of how these medical conditions develop.

By using a combination of genetic and brain imaging studies, our study has illuminated some of the fundamental biology of what leads to left-handedness in humans. We discovered intriguing links between handedness, genes relating to the cytoskeleton, language-related areas of the brain, and diseases such as schizophrenia and Parkinson's. Left-handedness, therefore, appears to be a consequence of the developmental biology of the brain, in part driven by the complex interaction of many genes.