“Differences arise at every level of the brain’s astonishingly intricate architecture, leading to variances in how we think, learn and behave and in our propensity for mental illness. Jumping genes may explain how some of these differences arise, even in identical twins.”

Variations in the genes we inherit from our parents ensure that each of our brains is wired differently. But even identical twins, who inherit the same set of genes, can differ markedly in their mental functioning, behavioral traits and risk of mental illness or neurodegenerative disease. From where do these differences arise?

Gage’s laboratory has identified a likely suspect in the hunt for an explanation for this mysterious variability in brain function: jumping genes. Such genes (also known as “retrotransposons”) can insert copies of themselves into other parts of the genetic code, making one neuron function very differently than its neighbor. Many such insertions may create a mosaic of cells possessing varying genetic operating instructions, which in turn could influence cognitive abilities, personality traits and susceptibility to neurological problems.

To better understand how jumping genes play a role in brain function, Gage and his colleagues have investigated the genetic underpinnings of Rett syndrome, a rare neurodevelopmental disease that affects mostly girls and is considered one of the autism spectrum disorders. Typical features of the disorder include loss of speech, stereotypic movements, mental retardation and social-behavioral problems. Although almost all cases are caused by a mutation in the MeCP2 gene, how severely people are affected by the symptoms of Rett syndrome varies widely.

Gage’s team found that a mutation in the MeCP2 gene mobilizes the L1 retrotransposons in brain cells of Rett syndrome patients, reshuffling their genomes. Their research showed that the mutation in the brains of mice with Rett syndrome resulted in a significant increase in numbers of L1 insertions in their neurons, suggesting that the jumping genes might account for some of the effects of the MeCP2 mutation. Using stem cell reprogramming techniques, the researchers generated neurons from skin cells of Rett syndrome patients, which they could then study in the laboratory. Similar to the findings in mice, these human neurons possessed high numbers of L1 copies, which might explain the variability in symptoms seen in people with the disorder.

Gage’s findings may not only explain how a single mutation can cause the baffling variability of symptoms typical of Rett syndrome but also shed new light on the complexity of molecular events that underlie other psychiatric disorders, such as autism and schizophrenia.

For more information, please visit www.salk.edu/faculty/gage