Researchers link genetic errors to schizophrenia

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A team of researchers at the University of Washington and Cold Spring Harbor Laboratories has uncovered genetic errors that may shed light on the causes of schizophrenia. The scientists found that deletions and duplications of DNA are more common in people with the mental disorder, and that many of those errors occur in genes related to brain development and neurological function. The findings, which were replicated by a team at the National Institute of Mental Health, appear in the March 27 online edition of the journal *Science*.

Schizophrenia, a debilitating psychiatric disorder, affects approximately 1 percent of the population. People with schizophrenia suffer from hallucinations, delusions, and disorganized thinking, and are at risk for unusual or bizarre behaviors. The illness greatly impacts social and occupational functioning and has enormous public health costs.

The team of investigators, led by Tom Walsh, Jon McClellan, and Mary-Claire King at the UW, and Shane McCarthy and Jonathan Sebat at Cold Spring Harbor, examined whether the genetic errors, which are individually rare DNA deletions and duplications, contribute to the development of schizophrenia.

Some deletions and duplications are common and found in all humans. The researchers studied such mutations that were found only in individuals with the illness, and compared them to mutations found only in healthy persons. They theorized that rare mutations found only in schizophrenic patients would be more likely to disrupt genes related to

brain functioning and thus may cause schizophrenia.

The study was conducted using DNA from 150 people with schizophrenia and 268 healthy individuals. The investigators found rare deletions and duplications of genes present in 15 percent of those with schizophrenia, versus only 5 percent in the healthy controls. The rate was even higher in patients whose schizophrenia first presented at a younger age, with 20 percent of those patients having a rare mutation.

The results were replicated by a second research team, led by Anjene Addington and Judith Rapoport at the National Institutes of Mental Health. They found a higher rate of rare duplications or deletions in patients whose schizophrenia began before age 12 years, a very rare and severe form of the disorder.

In individuals with schizophrenia, mutations were more likely to disrupt signaling genes that help organize brain development. Each mutation was different, and impacted different genes. However, several of the disrupted genes function in related neurobiological pathways.

The findings suggest that schizophrenia is caused by many different mutations in many different genes, with each mutation leading to a disruption in key pathways important to a developing brain. Once a disease-causing mutation is identified, other different disease-causing mutations may be found in the same gene in different people with the illness.

Thus, for most cases of schizophrenia, the genetic causes may be different. This observation has important implications for schizophrenia research. Currently, most genetic studies examine for mutations that are shared among different individuals with the illness. These approaches will not work if most patients have different mutations causing their condition.

Fortunately, there are now genomic technologies available that allow researchers to discover rare mutations within each individual with a disorder. As these technologies improve, it will be possible to detect other types of disease-causing mutations. Eventually, the identification of genes disrupted in individuals with schizophrenia will allow the development of new treatments more specifically targeted to disrupted pathways.

Source: University of Washington

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