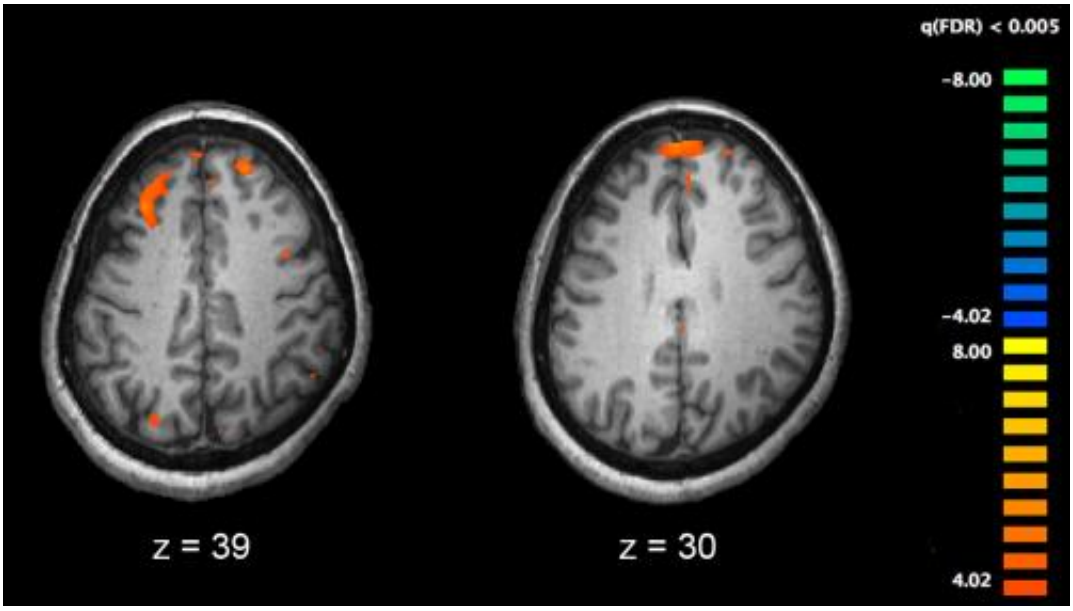
Rare mutations found to increase risk of schizophrenia and shortened school stays

October 4 2016, by Bob Yirka



Functional magnetic resonance imaging (fMRI) and other brain imaging technologies allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in orange, during an fMRI study of working memory. Credit: Kim J, Matthews NL, Park S./PLoS One.

(Medical Xpress)—Two teams of researchers looking to better understand what happens to people born with certain rare genetic mutations have found a link between an increased risk of schizophrenia and how long such people remain in school. In one of the studies, a team

made up of researchers from several institutions in the U.S. and Sweden conducted a study of gene mutations in a large group of Swedish people, some of whom had been diagnosed with schizophrenia and compared them with schizophrenia rates. The other group conducted a similar analysis with a large group of people from Finland, Estonia and Sweden looking for a connection between gene mutations and school dropout rates.

Both teams have published their results in the journal *Nature Neuroscience*.

In the first study, the researchers looked at protein encoding sequences of DNA, focusing on rare mutations that did not appear in people who had never been diagnosed with a psychiatric illness. In so doing, they were able to see that the mutations were more common in those people that had been diagnosed with schizophrenia. They also found that the mutations were involved in the expression of proteins in the synapses of brain cells. These finding, the researchers suggest, indicate that such mutations play at least some role in the development of schizophrenia.

In the other study, the researchers looked at similar rare mutations, but compared them to the amount of time that people stayed in school. They found that one such mutation could be linked with three fewer months of school attendance by those that had it than by students in the general population. For other people who had the rare mutations—specifically in parts of their brains—the researchers found a difference of six months less school attendance.

Both teams note that they do not believe a single factor such as a person having a rare mutation is solely responsible for the development of brain disorders such as schizophrenia or for the amount of time a student remains in school—rather, both are suggesting that rare gene mutations may be one of the factors involved, along with other influences such as

the environment in which people live.

More information: Giulio Genovese et al. Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia, *Nature Neuroscience* (2016). DOI: 10.1038/nn.4402

Abstract
By analyzing the exomes of 12,332 unrelated Swedish individuals, including 4,877 individuals affected with schizophrenia, in ways informed by exome sequences from 45,376 other individuals, we identified 244,246 coding-sequence and splice-site ultra-rare variants (URVs) that were unique to individual Swedes. We found that gene-disruptive and putatively protein-damaging URVs (but not synonymous URVs) were more abundant among individuals with schizophrenia than among controls ($P = 1.3 \times 10^{-10}$). This elevation of protein-compromising URVs was several times larger than an analogously elevated rate for de novo mutations, suggesting that most rare-variant effects on schizophrenia risk are inherited. Among individuals with schizophrenia, the elevated frequency of protein-compromising URVs was concentrated in brain-expressed genes, particularly in neuronally expressed genes; most of this elevation arose from large sets of genes whose RNAs have been found to interact with synaptically localized proteins. Our results suggest that synaptic dysfunction may mediate a large fraction of strong, individually rare genetic influences on schizophrenia risk.

Andrea Ganna et al. Ultra-rare disruptive and damaging mutations influence educational attainment in the general population, *Nature Neuroscience* (2016). DOI: 10.1038/nn.4404

Abstract
Disruptive, damaging ultra-rare variants in highly constrained genes are enriched in individuals with neurodevelopmental disorders. In the

general population, this class of variants was associated with a decrease in years of education (YOE). This effect was stronger among highly brain-expressed genes and explained more YOE variance than pathogenic copy number variation but less than common variants. Disruptive, damaging ultra-rare variants in highly constrained genes influence the determinants of YOE in the general population.