Selection on genes underlying schizophrenia during human evolution

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Several genes with strong associations to schizophrenia have evolved rapidly due to selection during human evolution, according to new research in the Proceedings of the Royal Society B.

Researchers found a higher prevalence of the influence of so-called positive selection on genes or gene regions known to be associated with the disorder than a comparable control set of non-associated genes, functioning in similar neuronal processes.

This is consistent with the theory that positive selection may play a role in the persistence of schizophrenia at a frequency of one per cent in human populations around the world, despite its strong effects on reproductive fitness and its high heritability from generation-to-generation.

It also provides genetic evidence consistent with the long-standing theory that schizophrenia represents, in part, a maladaptive by-product of adaptive changes during human evolution - possibly to do with aspects of creativity and human cognition.

“The world-wide presence of this disorder at an appreciable frequency, despite its impact on human health and reproductive fitness, is somewhat of a paradox,” said Dr Steve Dorus from the University of Bath, who worked with Dr Bernard Crespi from Simon Fraser University (Canada) and Dr Kyle Summers from East Carolina University (USA) on the research.

“This may be explained by the existing theory that the condition represents, in part, a by-product of adaptive changes during human evolution.

“Our finding that positive evolutionary processes have impacted genes underlying the disorder is consistent with this idea.

“However, the selective forces influencing the evolution of these genes remain unknown.

“Given the complex genetic nature of the condition, selection may be mediated by a diverse array of neurodevelopmental, neurophysiological and psychological mechanisms.

“Schizophrenia has also been associated with creativity throughout recorded history, but whether this link has a genetic basis is certainly not yet clear.”

The researchers analysed the molecular evolution of the 76 genes that have the strongest genetic association with the disorder.

They surveyed human polymorphisms - discrete changes in the human genome that vary between individuals - for very recent selective events within specific human populations.

They also compared genes between mammalian species to identify selection on primate lineages salient to the evolution of humans and the disorder.

The research identified evidence for positive selection on a variety of genes, including three genes that have the best functional or reproducible associations with the disorder: disrupted in schizophrenia (DISC1), dystrobrevin-binding protein 1 (DTNBP1) and neuregulin 1 (NRG1).

“For the first time it is possible to complement our genetic understanding of the disorder with substantial evolutionary and comparative genomic analyses,” said Dr Dorus.

“Decades of intensive research, using association and inheritance studies between affected and non-affected siblings, has resulted in a much clearer understanding of the genetic basis of the disorder.

“Hopefully, a better understanding of the evolution

of the substrates underlying the disease will assist in characterizing how they are dysregulated in the disorder.

“Understanding the impact of positive selection may also help refine hypotheses concerning genetic links between schizophrenia and aspects of human creativity and cognition.

Source: University of Bath