Autism Genes Exist in Us All

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A new study has found that genetic factors underlying autism are present in everyone and are influencing our behaviour.

How genetically different are individuals diagnosed with autism compared with non-autistic people in the general population? According to a new study into the genetics of autistic spectrum disorder (ASD), there may be more similarities than previously thought.

ASD is a neurodevelopmental condition characterised by deficits in social behaviour and communication, along with restrictive and repetitive interests. They may include elements such as a lack of understanding of non-verbal communication, difficulties with social interaction, repetitive motor movements and speech, fixation with routines, particular foods and unusual objects, and extreme distress at small changes.

ASD is estimated to occur in around 1% of people worldwide. It's thought to be caused by a combination of different genetic and environmental factors yet, despite extensive research over the past decade, its exact causes are not fully understood.

For thousands of rare diseases, genetic causes can be pinned down to a single genetic factor that has a large and detrimental biological impact. In Huntington's disease, for example, a single gene mutation causes severe neurodegeneration and brain damage.

But this is not the case for nearly all common diseases, including asthma, heart disease, diabetes, arthritis and inflammatory bowel disease. For these common diseases the evidence points firmly to the existence of numerous genetic factors – often in the order of many thousands. In these cases, each genetic factor on its own has a tiny impact but, added together, they influence disease.

This is what has been found for ASD, where thousands of small genetic factors seem to be acting together in combination to produce a detectable difference in ASD-related traits.

Over the years, scientists discovered that almost all genetic risk factors that have been found for ASD can also be found in unaffected people from the general population. However, the effects of these genetic risk factors in non-autistic individuals were previously unknown. Until now.

In a recent study published in *Nature Genetics* (http://tinyurl.com/z2hg6qo) a team of international researchers, including Prof David Evans of the University of Queensland's Diamantina Institute, studied thousands of autistic and non-autistic individuals from all around the world. The researchers wanted to find out what impact genetic factors for ASD have in the general population. To do so, they analysed genetic data from individuals diagnosed with autism, together with data from British children in the general population whose social and communication skills had been assessed.

They discovered that around one-quarter of the genetic factors

contributing to ASD also influenced social and communication abilities in the non-autistic children in the study. This was the case for two different types of genetic factors: inherited genetic mutations, which your parents pass down to you, and also new genetic mutations that spontaneously arise – they aren't present in either parent. The study found that both new and inherited genetic mutations involved in ASD influenced social and communication abilities in the general population.

"Many of the genes that increase the risk of ASD are also present in healthy individuals and indeed appear to contribute to traits that we typically consider to be part of normal functioning, such as our ability to communicate and socially interact with others," Evans explains. "In reality everybody can be placed on a spectrum, determined by their genetic and environmental makeup, and one can think of ASD as being at the far end of the spectrum."

This is considered a step forward in the understanding of ASD, as they have typically been considered a binary condition that is either present or absent in a person. However, these new findings show that genetically-influenced traits involved in ASD are actually present in all individuals to varying degrees.

Across the general population there is a wide variety of ability levels for social interaction and communication. These levels are determined by a combination of many different genetic factors, environmental factors and chance events. The study revealed that there is a continuum of different capability levels for social and communication skills, with each of us standing somewhere in that continuum.

"Many traits that relate to disease risk, like blood pressure and cholesterol, demonstrate a similar continuum of risk," says study co-author Prof George Davey Smith of the University of Bristol. "The present study demonstrates how this continuum applies to ASD, a condition generally thought of as either existing or not."

According to Prof Andrew Whitehouse, head of autism research at the University of Western Australia, the study has "fascinating implications for the concept of 'autism'. The research clearly shows that nature doesn't draw a neat dividing line between 'autism' and 'not autism', even at a genetic level. As health professionals, we need to always acknowledge that we are the ones that generate the arbitrary diagnostic 'line in the sand', and that in reality that line is very fuzzy."

The question of how clinical thresholds for a diagnosis of ASD should be established has been cause for much discussion, particularly among clinical practitioners. As part of a series on autism published this year in *Lancet Neurology*, Prof John Constantino of Washington University referred to tensions between clinical judgements about where these thresholds should lie and the criteria for ASD described by the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). He argued that a compelling case can be made for adopting percentile-based thresholds for ASD criteria, much like IQ scales for intellectual disability. Certainly, the genetic findings of the *Nature Genetics* study adds to the debate surrounding whether diagnostic procedures for ASD may be improved by focusing on continuum-based traits.

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The study findings hold promising implications for the future of ASD research. First, it suggests that studying the behavioural traits of people in the general population could lead to new insights into what causes ASD. For example, determining the genetic factors and biological processes in normally-developing children may help to determine processes that are disturbed in children diagnosed with ASD. This has the huge advantage that any individual from the general population can be studied, and finding individuals diagnosed with ASD will not necessarily be required.

A second exciting prospect is that very large studies of the genetic causes of ASD-related traits could be undertaken much more easily by studying traits in the general population. While a handful of specific genetic mutations have already been linked to ASD, this number falls far short of the thousands believed to be implicated in the condition. The lack of known specific genetic factors for ASD is at least partly due to the fact that the very small individual genetic effects cannot be detected from studies of the sizes that are currently available.

This is because for genetic studies of common diseases, extremely large numbers of people are needed to uncover these small, specific genetic effects. In some cases, hundreds of thousands of people would be required. While this number would be difficult to achieve for a study of ASD individuals, this is largely feasible if scientists were able to study individuals in the general population.

Essentially, undertaking future ASD-related research in large numbers of the general population could potentially address some of the existing issues of study size currently limiting genetic studies of ASD. This could lead to the discovery of vastly more genetic factors for ASD-related traits.

Beyond ASD, studying continuum-based behavioural traits that affect the whole population also holds encouraging prospects for many other neurological and psychiatric diseases. Hence the new study could lead to improved genetic research for many complex and elusive neuropsychiatric conditions, such as schizophrenia.

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