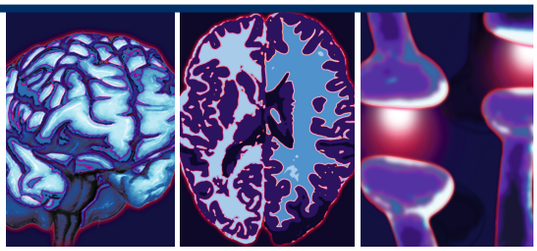
"The results from these studies, and others like them, could identify genes involved in the development of autism spectrum disorders, which would allow advances in both the diagnosis and classification of autism spectrum disorders and potential therapies for the disorders."



New genes found with a link to autism

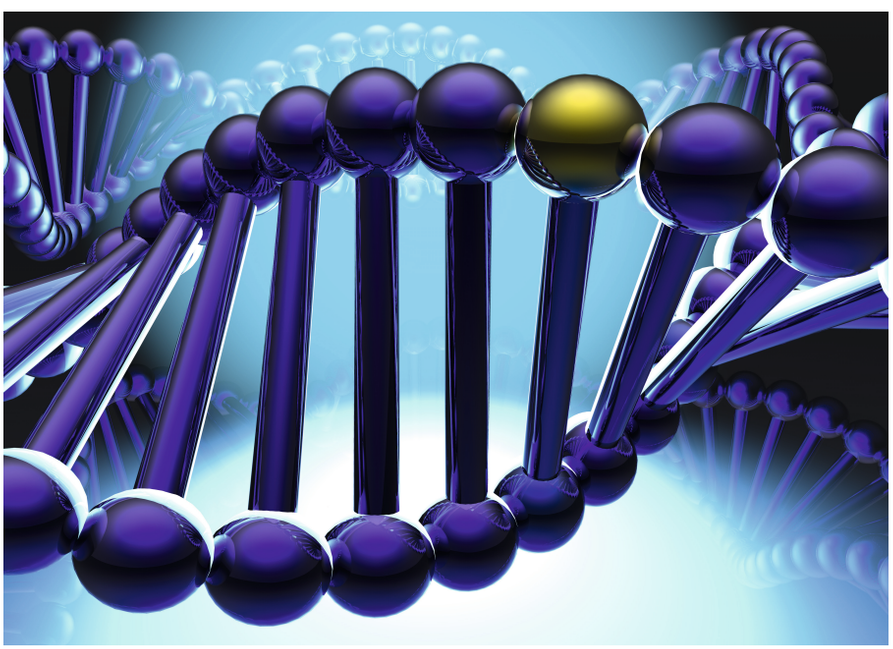
New genes have been found by whole-exome sequencing that are linked to the development of autism

Three papers recently published in *Nature* reveal mutations in at least three proteins that can be linked to autism spectrum disorders (ASDs) through work by the Autism Sequencing Consortium. The papers suggest that *de novo* mutations are a common risk factor for the development of ASDs.

Three proteins, SCN2A, CHD8 and KATNAL2 stood out as having mutations that are highly linked to a risk of developing autism. However, mutations were also discovered in more than 200 other proteins that may be involved in some way towards the development of ASDs.

Researchers from multiple institutions took part in the study, including Yale University School of Medicine (CT, USA), Harvard Medical School (MA, USA), Mount Sinai School of Medicine (NY, USA) and University of Washington School of Medicine (WA, USA).

The three studies all used whole-exome sequencing, analysis of only the protein coding exons of the genome, to determine mutations in genes that were found in individuals with ASDs. The combined studies looked at the genomes from 580 families with a child with an ASD, but with no family history of autism. This enabled



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researchers to look for *de novo* mutations, ones that are not found in either parent but have newly occurred in their children.

Neale *et al.* demonstrated that the rate of *de novo* mutations found throughout the genome was slightly higher in affected individuals than in their unaffected families. While many of these mutations will not affect the risk of autism, a study of the protein–protein interactions of the gene products found that proteins that had mutations were more likely to interact with each other.

The authors suggest that these results "support polygenic models in which spontaneous coding mutations in any of a large number of genes increases risk by five- to 20-fold."

Joseph Buxbaum, from Mount Sinai School of Medicine and lead author of the study, explains that, "We now have a good sense of the large number of genes involved in autism and have discovered about 10% of them."

Mark Daly, a co-author from Harvard Medical School, said: "These genes hold key insights into the true biological causes of autism – insights we have been unable to gain through other lines of research."

The study by O'Roak *et al.* found that mutations were much more likely to be passed from the father, with paternal mutations four-times as prevalent as maternal ones. This confirms previous theories that autism risk has a paternal bias.

The third study compared results of individuals with ASDs with their unaffected siblings. The researchers suggest that their method allows the identification of autism risk genes, and demonstrated a high likelihood that mutations in the *SCN2A* gene impart a risk of developing an ASD.

Autism affects one in every 88 in the USA, with men more often affected than women. The causes of autism are thought to be due to a complex interplay of genetic and environmental factors, with many genes involved in determining risk.

This has significant consequences for autism research; Buxbaum thinks that "As these genes are further characterized, this will lead to earlier diagnosis and novel drug development. This work is crucial for advancing autism treatment."

The results from these studies, and others like them, could identify genes involved in the development of ASDs, which would allow advances in both the diagnosis and classification of ASDs and potential therapies for the disorders.

Sources: Sanders SJ, Murtha MT, Gupta AR *et al. De novo* mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature* doi:10.1038/nature10945 (2012) (Epub ahead of print); O'Roak BJ, Vives L, Girirajan S *et al.* Sporadic autism exomes reveal a highly interconnected protein network of *de novo* mutations. *Nature* doi:10.1038/nature10989 (2012) (Epub ahead of print); Neale BM, Kou Y, Liu L *et al.* Patterns and rates of exonic *de novo* mutations in autism spectrum disorders. *Nature* doi:10.1038/nature11011 (2012) (Epub ahead of print).

Study suggests three genes are associated with post-traumatic stress disorder

A study recently published in the *Journal of Affective Disorders* has suggested that two genes, *TPH1* and *TPH2* and a common polymorphism, *5HTTLPR*, associate with symptoms of post-traumatic stress disorder (PTSD) and depression in individuals who have experienced traumatic events.

Researchers from University of California, Los Angeles (CA, USA) studied multiple generations of 12 families who were affected by the 1988 Spitak earthquake in Armenia.

Two hundred individuals, from up to five generations of a family, were assessed for symptoms of PTSD and depression as well as the severity of their exposure to the trauma.

An association was found between the 't' alleles of both the *TPH1* and *TPH2* genes and PTSD symptoms. These genes play an important part in the conversion of tryptophan to serotonin, a neurotransmitter whose activity is linked to mood and sleep regulation.

Armen Goenjian, lead author of the study says, "We suspect that the gene variants produce less serotonin, predisposing these family members to PTSD after exposure to violence or disaster."

The third association implicates a polymorphic region of the *SLC6A4* gene, *5HTTLPR,* as important in altering the risk of developing depressive symptoms. The gene encodes the serotonin transporter, also important in the regulation of serotonin activity.

The researchers postulate that finding genes that relate to PTSD and depression will allow new discoveries in this area of research, by implicating biological mechanisms in the pathology of this disorder that have not been previously elucidated.

Goenjian also envisages other potential uses for these findings. As he explains, "A diagnostic tool based upon *TPH1* and *TPH2* could enable military leaders to identify soldiers who are at higher risk of developing PTSD, and reassign their combat duties accordingly."

In the future, the researchers are looking to see if these findings are true for different racial groups. According to Goenjian; "Our next step will be to try and replicate the findings in a larger, more heterogeneous population."

Source: Goenjian AK, Bailey JN, Walling DP *et al.* Association of *TPH1*, *TPH2*, and *5HTTLPR* with PTSD and depressive symptoms. *J. Affect. Disord.* doi:10.1016/j.jad.2012.02.015 (2012) (Epub ahead of print).

Alternative classification system for autism may allow a more rapid diagnosis

Autism diagnosis is usually a slow process, and must be performed by a clinical practitioner. Researchers at Harvard Medical School (MA, USA) have developed an alternative system for diagnosing autism spectrum disorders (ASDs), using machine-learning algorithms in an artificial intelligence setting.

Currently, the main tools for the diagnosis of ASDs are the Autism Diagnostic Observation Schedule-Genetic (ADOS) and the Autism Diagnostic Interview, which is a survey involving 93 questions; both can take hours to reach a diagnosis.

The alternative system, developed by Dennis Wall and colleagues, involves more streamlined versions of these systems to allow a diagnosis in a much shorter time frame.

The researchers analyzed the ADOS to find the most important items in module one, the module of the ADOS used for the diagnosis of young children. They used this to produce a new classifier that uses artificial intelligence techniques to allow machines to make decisions.

They then tested the classifier against more than 400 individuals from the Boston Autism Consortium and the Autism Genetic Resource Exchange. The results show that the new classifier performs at almost 100% accuracy. In addition to producing a diagnosis, the classifier also provides a measure of confidence in the diagnosis.

As well as being faster, the new classification system, which can use a short video of the individual being diagnosed, may be an easier option for an initial diagnosis in more remote areas, reducing the need to travel to a suitable diagnostic center.

As autism therapies produce better results when started early, it is important to be able to diagnose individuals with ASDs as young as possible.

Wall hopes that the increased speed and accessibility of this approach "will make it possible for more children to be accurately diagnosed during the early critical period when behavioral therapies are most effective."

Wall explains the significance of the findings; "This approach is the first attempt to retrospectively analyze large data repositories to derive a highly accurate, but significantly abbreviated, classification tool."

The aim for the future is that "the parent or caregiver will be able to take the crucial first steps to diagnosis and treatment from the comfort of their own home and in just a few minutes."

Source: Wall DP, Kosmicki J, Peluca TF, Harstad E, Fusaro VA. Use of machine learning to shorten observation-based screening and diagnosis of autism. *Translational Psychiatry* doi:10.1038/tp.2012.10 (2012) (Epub ahead of print).

Can the temperament of a toddler predict gambling problems in later life?

A new study, published in *Psychological Science*, has suggested a link between 3-year-old children displaying moody or restless behaviors and the likelihood of their developing gambling problems in later life.

First author, Wendy Slutske, from the University of Missouri (MO, USA), spoke about the implications of the study to *Neuropsychiatry*; "The significance of this work is establishing that observable individual differences that are related to later gambling problems are onboard early in life, as early as the preschool years."

The researchers assessed over 1000 individuals at the age of 3 years to classify them into one of five categories, including undercontrolled, confident and well adjusted. Participants were then asked to answer two questionnaires about gambling behaviors at the ages of 21 and 32.

While over 80% of the individuals had gambled by the age of 21, only 13% of these had 'disordered' gambling, defined by the presence of problems such as a need to gamble or financial or personal difficulties as a result of gambling.

For these 'disordered' gamblers, an undercontrolled temperament at age 3 was a significant predictor of their gambling, with other factors such as childhood intelligence and socioeconomic status also important.

Slutske stresses that only a few individuals actually go on to develop a gambling problem, and that "an undercontrolled 3-year old is not doomed to become an adult problem gambler; they are just at increased risk."

According to Slutske, the researchers are "continuing to try to sort out why undercontrolled temperament in early childhood is related to later disordered gambling in adulthood." She continues, saying that this includes studying "whether undercontrolled children start to gamble at a younger age" as well as "whether there are overlapping sets of genetic risk factors that are associated with both disordered gambling risk and individual differences in personality."

Source: Slutske WS, Moffitt TE, Poulton R, Caspi A. Undercontrolled temperament at age 3 predicts disordered gambling at age 32: a longitudinal study of a complete birth cohort. *Psychol. Sci.* doi:10.1177/0956797611429708 (2012) (Epub ahead of print).

One step closer to discovering the mechanisms that lead to psychosis

Childhood trauma, such as sexual abuse or bullying, significantly increases the chance of developing psychosis as an adult, according to a new study

New research, published in *Schizophrenia Bulletin* and involving researchers from the University of Liverpool (UK) and Maastricht University (The Netherlands), provides more evidence that psychotic conditions, such as schizophrenia and bipolar disorder, are heavily impacted by environmental factors, particularly trauma during childhood.

The study analyzed results from 27,000 previous papers to draw conclusions about the effects of trauma at a young age on symptoms of psychosis in adulthood.

The results provide evidence for current theories of the origins of psychotic symptoms, including hallucinations and paranoia, suggesting that, contrary to previous hypotheses, environmental influences are very important in the development of these conditions, and must be considered in addition to genetic predispositions.

Childhood trauma, including sexual abuse, bullying, physical trauma, losing a parent and institutional care, increases the risk of developing psychoses in later life by an average of three-times, increasing to 50-times in severe cases.

Richard Bentall, first author of the study from the University of Liverpool, said that the results "suggest that studies on the neurological and genetic factors associated with these conditions, which are not yet fully understood, are more likely to advance our knowledge if we take into account a patient's life experiences."

He stresses that "We need to know, for example, how childhood trauma affects the developing brain, as well as whether there are genetic factors that increase vulnerability or resilience to traumatic events."

This has important implications for clinicians during diagnosis and treatment of psychotic disorders; as well as recording genetic or familial risk factors, clinicians should put emphasis on learning more about the historical background of their patients.

Bentall explains that "Now that we know environment is a major factor in psychosis and that there are direct links between specific experiences and symptoms of the condition, it is even more vital that psychiatric services routinely question patients about their life experience." He continues; "Surprisingly, some psychiatric teams do not address these issues and only focus on treating a patient with medication."

Another important finding from the study is that particular types of trauma more often lead to certain psychoses, providing insights into the mechanisms behind the development of psychosis. For example, abuse was more likely to lead to hallucinations, but disrupting relationships during childhood lead to symptoms of paranoia.

Future research will focus on a better understanding of the mechanisms that lead to the development of psychosis, as well as looking into why there is such a large time difference between trauma and the resulting psychotic symptoms.

Source: Bentall RP, Wickham S, Shevlin M, Varese F. Do specific early-life adversities lead to specific symptoms of psychosis? A study from the 2007 The Adult Psychiatric Morbidity Survey. *Schizophr. Bull.* doi:10.1093/schbul/sbs049 (2012) (Epub ahead of print).

– All stories written by Alisa Crisp

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