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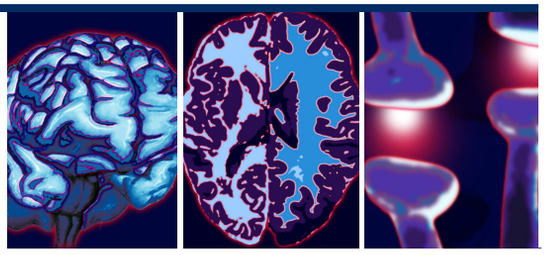


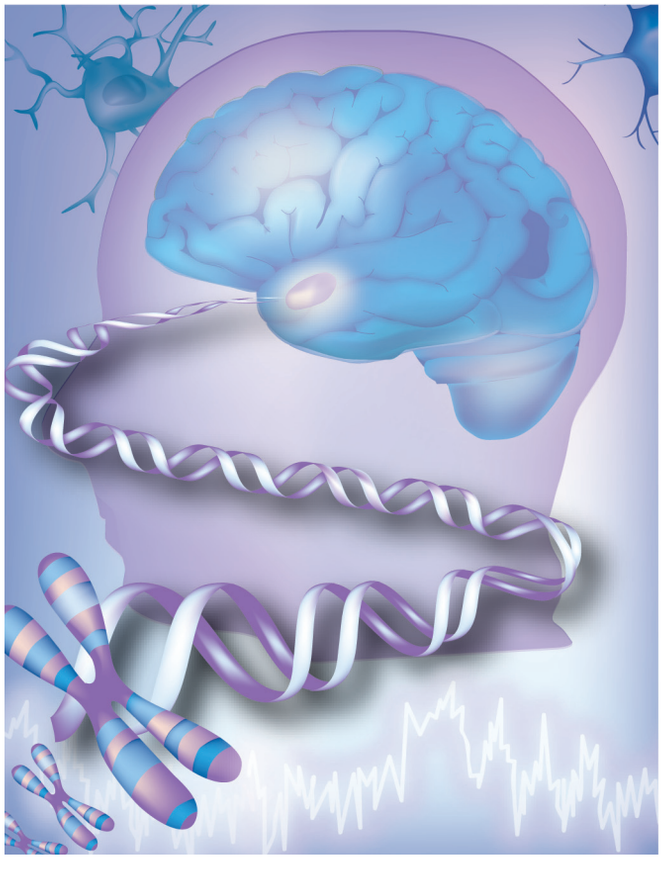
New study sheds light on genetic susceptibility to autism and other neuropsychiatric conditions

Researchers at the University of Toronto and the Hospital for Sick Children (Toronto, Canada) successfully identified *de novo* and rare copy-number variations (CNVs) in 248 unrelated attention deficit–hyperactivity disorder (ADHD) patients using million-feature genotyping arrays, providing support for a role for rare CNVs in ADHD risk and reinforcing evidence for the existence of common underlying susceptibility genes for ADHD, autism spectrum disorder (ASD) and other neuropsychiatric disorders. The study is published on 10 August advance online edition of *Science Translational Medicine*.

Microarrays were used to study the DNA of the 248 participants who were unrelated patients with ADHD. Spontaneous CNVs were found in three of the 173 children (1.7%) for whom both parents' DNA were available; this occurs when the parents are not affected by ADHD and the mutations in their child are not genetically inherited. These CNVs affected brain-expressed genes *DCLK2*, *SORCS1*, *SORCS3* and *MACROD2*. A total of 19 of the 248 patients (7.7%) were diagnosed with rare CNVs that were inherited from the parents.

The researchers then used the same microarrays to test for rare CNVs in an independent, recently collected group of 349 unrelated patients with a primary diagnosis of ASD. The aim was to further explore the overlap of risks in ADHD and ASD. They found that deletions of the neuronal ASTN2 and the ASTN2-intronic *TRIM32* genes bore the strongest association with ADHD and ASD. However, several other shared candidate genes were also discovered.

Speaking to *Neuropsychiatry*, Stephen Scherer, senior scientist and director of The Center for Applied Genomics at SickKids and the McLaughlin Centre and professor in the Department of Molecular Genetics at the University of Toronto, explained: "In the first study of it's kind we've tested for *de novo* and rare inherited CNVs in ADHD and using this technique have identified a few new ADHD candidate genes. Interestingly, we've also found that some of the 'ADHD genes' are also the same ones identified as risk factors in ASD. So people carrying the same CNVs can have different symptoms, and it's not always the same risk and the clinical presentation can vary".



Russell Schachar, senior scientist and psychiatrist at SickKids and professor of psychiatry at the University of Toronto, commented: "It's not always the same risk. As we've seen in autism and other conditions, relatively few of these CNV's repeat in affected individuals". Schachar adds, "A lot of these associated problems probably arise from the fact that they

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are sharing genetic risk for different conditions". Most ADHD sufferers also have at least one other condition, such as anxiety, mood, conduct or language disorders. Up to 75% of people with ASD also have attention deficits or hyperactivity.

"These are probably genetic factors that increase the risk for various kinds of neuropsychiatric disorders and it poses a huge challenge to us to figure out what makes an ADHD case and what makes an ASD case. There are lots of different possibilities to explain why some common risks can manifest into different kinds of disorders", Schachar explains. He went on to add that while the new study observed this phenomenon, more research will be required to the determine the cause.

Commenting on the future direction of this research, Schachar explains: "There is much to do to confirm that the CNVs that we have identified are truly causal in ADHD and to figure out how the disorder arises from the genetic variant. That work will involve further studies of families who are transmitting a CNV. In the future, we see a role for genetic analysis in the early diagnosis of ADHD and in treatment planning".

Source: Lionel AC, Crosbie J, Barbosa N *et al.* Rare copy number variation discovery and cross-disorder comparisons identify risk genes for ADHD. *Sci. Transl. Med.* 3(95), 95RA75 (2011).

Frequent use of tanning beds could lead to addiction

A novel pilot study has investigated the effect of regular tanning bed use on visitors, demonstrating that their brains and behaviors show similar changes to those of addicts. The study, conducted by researchers at UT Southwestern Medical Center (TX, USA), revealed that tanning bed users have similar brain activity and corresponding blood flow to those in drug and alcohol addicts.

> "The results demonstrated an increased blood flow in the dorsal striatum, anterior insula and medial orbitofrontal cortex of the brain during the ultraviolet radiation session relative to the session in which the ultraviolet rays were blocked."

Participants in the study used tanning beds in two consecutive events. In the first block the participants were exposed to ultraviolet radiation, and in the second trial their exposure to ultraviolet radiation was blocked by filters. The participants were not made aware of whether they received ultraviolet exposure or not in the sessions. Before and after each session, the participants were asked how much the idea of tanning appealed to them. Throughout the sessions the users were administered a specific radioisotope; allowing scientists to measure their brain blood flow during the tanning session. The aim of the experiment was to measure the rewarding properties of ultraviolet radiation. The focus was on assessing the effects of a commercially available tanning bed by measuring the cerebral blood flow, a measure of brain activity. This was done with the use of SPECT.

The results demonstrated an increased blood flow in the dorsal striatum, anterior insula and medial orbitofrontal cortex of the brain during the ultraviolet radiation session relative to the session in which the ultraviolet rays were blocked. Typically, these brain regions are associated with the experience of reward. It was concluded from the study that ultraviolet radiation may have centrally rewarding properties that encourage frequent tanning, despite the risk of dangerous skin diseases.

Bryon Adinoff, professor of psychiatry and senior author of the study, explained to *Neuropsychiatry*: "This preliminary study suggests that ultraviolet rays from a tanning bed, similar to those received from sunlight, can activate brain regions associated with reward. If ultraviolet rays can be rewarding, then it may have the potential to become addictive".

According to the Skin Cancer Foundation, approximately 120,000 cases of melanoma are diagnosed in the USA alone every year. Users under the age of 30 years who regularly visit the tanning bed ten times a year have eight-times the risk of developing lethal melanoma.

> "If ultraviolet rays can be rewarding, then it may have the potential to become addictive."

Adinoff further explained to *Neuropsychiatry*: "If future work demonstrates that certain compulsive tanners show brain changes consistent with other addictive disorders, it would suggest a different framework would be needed for treating compulsive tanners.

"This study did not compare compulsive tanners to noncompulsive tanners, so we cannot say from this study that the two populations are different in their brain response to ultraviolet rays".

The results of the present study are particularly important given the increasing frequency of people using tanning beds, combined with the increasing public awareness of the dangers of exposure to ultraviolet rays.

Source: Harrington CR, Beswick TC, Graves M *et al.* Activation of the mesostriatal reward pathway with exposure to ultraviolet radiation (UVR) vs. sham UVR in frequent tanners: a pilot study. *Addict. Biol.* doi: 10.1111/j.1369-1600.2010.00312.x (2011) (Epub ahead of print).

Younger siblings of children with autism at greater risk of developing autism than previously thought

Children with older siblings who have been diagnosed with autism are under a significantly higher risk of being diagnosed with the same condition themselves than previously predicted, a multisite study led by researchers at the UC Davis Institute (CA, USA) has revealed. The investigators found that the probability of a younger sibling of a child with autism developing an autism spectrum disorder is 18.7%. They found that the risk of recurrence was over 26% for male infants and over 32% for young children with more than one older sibling who has been diagnosed with autism.

Autism is a neuropsychiatric disorder that typically affects a patient's ability to interact in a socially normal fashion, in addition to difficulties in learning and movement. The US CDC suggests that the incidence of autism is approximately one in 110 children, while the chance that a child who has an older sibling with autism will also develop autism was estimated to be between 3 and 10%. However, previous research was limited by small sample sizes and biases related to ascertainment, reporting and stoppage factors. The results of this study indicate that the actual probability is substantially higher.

"This is the largest study of the siblings of children with autism ever conducted", explained Sally Ozonoff, professor of psychiatry and behavioral sciences at the MIND Institute at UC Davis and the study's lead author. "There is no previous study that identified a risk of recurrence that is this high".

The study's participants were admitted into separate studies that were all part of the Baby Siblings Research Consortium. This is an international network that provides data from individually funded research sites to expedite further study into infants at high risk of developing autism due to an older sibling with the condition. A total of 12 consortium sites that are situated in the USA and Canada participated in the study, as well as other sites in countries such as Israel.

Although the overall rate of autism spectrum outcomes for all of the participants was 18.7%, there was a significant difference in the recurrence rate based on the amount of siblings the child had. If there was one older child with autism, the chances of the younger sibling being

New results suggest that most cases of schizophrenia are not inherited from parents

A study led by researchers at Columbia University Medical Center (NY, USA) suggests that many incidences of schizophrenia are not due to the simple inheritance of genes from parents. Maria Karayiorgou and Joseph Gogos led a group that studied the genomes of patients who were diagnosed with schizophrenia. They also studied the genomes of the patients' families as well as groups of healthy people. All of the participants were from the European-descent Afrikaner population of South Africa.

Over 15 years ago, Karayiorgou and her colleagues described a rare *de novo* mutation that accounted for 1–2% of sporadic cases of schizophrenia. Due to advances in technology, 3 years ago the group was able to examine the entire genome for corresponding lesions that insert of remove small sections of DNA; 10% of sporadic cases were accounted for by the mutations.

Using 'deep sequencing' they examined the nucleotide bases of almost all the genes in the human genome. They hoped to find if other mutations accounted for an even greater percentage of sporadic cases. In this study, they found 40 mutations that were from different genes, with the majority of these responsible for protein alteration.

"Identification of these damaging *de novo* mutations has fundamentally transformed our understanding of the genetic basis of schizophrenia", says Bin Xu, assistant professor of clinical neurobiology at Columbia University Medical Center and first author of the study.

The results of the study increase understanding of the persistence of schizophrenia despite the lack of genetic inheritance in most cases, and the high global risk of being diagnosed with the disease despite large environmental alterations.

Karayiorgou explains: "The fact that the mutations are all from different genes is particularly fascinating. It suggests that many more mutations than we suspected may contribute to schizophrenia. This is probably because of the complexity of the neural circuits that are affected by the disease; many genes are needed for their development and function".

Researchers believe that a necessary step towards understanding how schizophrenia develops involves finding perhaps hundreds more rare protein-altering genetic mutations that contribute to these cases. Karayiorgou and her team will now search for recurring mutations, which may potentially provide evidence that specific mutations contribute to schizophrenia.

Source: Xu B, Roos JL, Deheimer P *et al.* Exome sequencing supports a *de novo* mutational paradigm for schizophrenia. *Nat. Genet.* 43(9), 864–868 (2011).

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diagnosed with autism was 20.1%, while 37% of the study participants had more than one sibling with autism. For these participants, the risk of developing autism rose to 32.2%.

"It's important to recognize that these are estimates that are averaged across all of the families. So, for some families, the risk will be greater than 18%, and for other families it would be less than 18%. At the present time, unfortunately, we do not know how to estimate an individual family's actual risk", Ozonoff further commented.

Speaking about the implications of the work, Ozonoff relayed: "This study shows that the younger siblings of children with autism spectrum disorders need to be tracked very carefully, and this may require more than the normal surveillance that a pediatrician might typically do. This should include very explicitly and regularly checking in with parents on whether developmental milestones are being reached".

Source: Ozonoff S, Young GS, Carter A *et al.* Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics* 128(3), E488–E495 (2011).

About the News

The News highlights some of the most important events and research.
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