Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

New autism genetic risk factors identified

New autism genetic risk factors identified

US researchers identify a hereditary and nonhereditary risk factor for autism

In recent reports, two separate genetic defects have been shown to be associated with autism. One of the defects, caused by spontaneous deletion or duplication of a segment of chromosome 16, has been shown to be present in approximately 1% of autistic children. Three independent groups have also reported an association between the contactin-associated protein-like 2 (*CNTNAP2*) mutation on chromosome 7 and autism.

Published online in the *New England Journal of Medicine*, the Autism Consortium, a multicenter team, reported a 100-fold increased risk of developing autism in people who had deletions or duplications of a specific segment of chromosome 16, region 16p11.2. The mutations were found in autistic children but not their parents, suggesting that the mutation is spontaneous.

The group used a high-resolution genomic copy-number variant analysis to examine chromosomes from families in which there was at least one autistic member as well as from people without the disorder. Deletions or duplications in 16p11.2 were found in 24 of 2252 people from families with at least one autistic member, compared with only two of 18,834 people without the disorder.

Large instances of noninherited chromosomal abnormalities are extremely rare, as Mark Daly, lead author of the study commented. "Finding precisely the same deletion in such a significant proportion of patients suggests that it is a very strong risk factor for autism."

The group is now attempting to identify the specific gene or genes involved in the mutation.

In three independent studies, published online in the *American Journal of Human Genetics*, researchers have confirmed an association between *CNTNAP2*, a gene previously identified in four Amish children in 2006, and risk of autism, in much larger samples.

Aravinda Chakravarti, of the Johns Hopkins University School of Medicine, who led one of the studies, explained their results. "We found a factor that is probably present in every autistic kid. But while it may be necessary, it is not sufficient by itself to cause the disease."

> "Finding precisely the same deletion in such a significant proportion of patients suggests that it is a very strong risk factor for autism."

"*CNTNAP2* is an excellent candidate gene for autism," Chakravarti commented. "It encodes a protein that's known to mediate interactions between brain cells and that appears to enable a crucial aspect of brain-cell development. A gene variant that altered either of these activities could have significant impact."

In another of the studies, Erik Puffenberger and colleagues built on their previous finding in Amish children. He commented. "This is a very exciting step for autism research. It also highlights the enormous potential of the 'small science' approach. Our initial work used only four affected Amish children. Careful study of these four patients uncovered the association between *CNTNAP2* and autistic behaviors. From that small beginning, *CNTNAP2* has now been implicated as a significant risk factor for autism."

Finally, Matthew State and colleagues identified a rare mutation in the same gene that was associated with autism and appeared to be inherited. "This convergence of rare and common variants in autism is unusual, but reinforces the growing consensus among genetics researchers that both types of changes in DNA sequence are going to be important contributors," State commented.

Dietrich Stephen, author of an accompanying commentary, is extremely positive about the findings and hopes that it may be possible to develop a diagnostic test for the *CNTNAP2* mutation. "The field of genetics is replete with examples where researchers are unable to reproduce results. Here we have independent confirmation in multiple groups using large samples sizes," he commented. "Now that the results of the initial *CNTNAP2* gene finding have been replicated, it strongly supports the notion that the 'broken version' of *CNTNAP2* is recognized as a cause of autism in the general population," he added.

Sources: Weiss LA, Shen Y, Korn JM *et al.* Association between microdeletion and microduplication at 16p11.2 and autism. *N. Engl. J. Med.* (2008) (Epub ahead of print);
Alarcón M, Abrahams BS, Stone JL *et al.* Linkage, association, and gene-expression analyses identify cntnap2 as an autism-susceptibility gene. *Am. J. Hum. Genet.* 82(1), 150–159 (2008);
Arking DE, Cutler DJ, Brune CW *et al.* A common genetic variant in the neurexin superfamily member cntnap2 increases familial risk of autism. *Am. J. Hum. Genet.* 82(1), 160–164 (2008);
Bakkaloglu B, O'Roak BJ, Louvi A *et al.* Molecular cytogenetic analysis and resequencing of contactin associated protein-like 2 in autism spectrum disorders. *Am. J. Hum. Genet.* 82(1), 165–173 (2008);
Stephan DA. Unraveling autism. *Am. J. Hum. Genet.* 82(1), 7–9 (2008).

 10.1586/14737175.8.2.177 ISSN 1473-7175

Psychiatric comorbidity shown to be very common

A recent study finds that the number of psychiatry outpatients who suffer from more than one psychiatric disorder is extremely high

Published in the February, 2008, issue of *Psychological Medicine*, researchers from Rhode Island Hospital (RI, USA) interviewed 2300 psychiatry outpatients to assess a wide range of psychiatric disorders.

The majority of the 2300 patients tested were found to have two or more disorders, and more than one third of the patients suffered from at least three disorders. The average number of current diagnoses per patient was 1.9. Patients with a principal diagnosis of post-traumatic stress disorder or bipolar disorder had the highest mean number of current comorbid disorders.

For almost half of the outpatients, major depressive disorder was the reason for seeking treatment. About 25% of the patients suffered from social phobia; but 95% of these diagnoses came from initial treatment for another disorder.

"…clinicians should assume that in outpatients presenting for the treatment of mood or anxiety problems, the patients have more than one diagnosis."

The lead author of the paper, Mark Zimmerman, Director of Outpatient Psychiatry at Rhode Island Hospital and Associate Professor of Psychiatry and Human Behavior at Brown Medical School (RI, USA) commented, "For disorders like social phobia that are infrequently diagnosed as the principle disorder in clinical practice, it will be important for the next generation of treatment-efficacy studies to determine if treatment is effective when the disorder is a comorbid condition."

The authors also hope that these results will encourage clinicians to check for comorbidity in psychiatric outpatients, as Zimmerman explained, "Based on the results of this study, clinicians should assume that in outpatients presenting for the treatment of mood or anxiety problems, the patients have more than one diagnosis."

Source: Zimmerman M, McGlinchey JB, Chelminski I, Young D. Diagnostic co-morbidity in 2300 psychiatric out-patients presenting for treatment evaluated with a semi-structured diagnostic interview. *Psychol. Med.* (2008) (Epub ahead of print).

Fast Track designation granted for CDX-110 for the treatment of glioblastoma multiforme

Drug:	CDX-110
Tradename:	NA
Manufacturer:	Celldex Therapeutics, Inc.
Indication:	Treatment of EGFRvIII-expressing glioblastoma multiforme

The US FDA has recently granted Celldex Therapeutics, Inc. (NJ, USA) Fast Track designation for their CDX-110 investigational immunotherapy for the treatment of EGFRvIII-expressing glioblastoma multiforme (GBM).

EGFRvIII, which is only found in cancerous tissue, is present in approximately 40% of GBM patients. CDX-110 immunotherapy works by activating a patient's immune system against EGFRvIII, therefore selectively attacking the tumor cells. Recent trials of the immunotherapy have shown highly promising results.

In the ACTIVATE Phase II study, patients with EGFRvIII-expressing GBM who were treated with CDX-110 had a median survival of 30 months, compared with only 14.5 months in historical controls. The median time to progression was also longer, at 13 months (p = 0.0001) in CDX-110-treated patients compared with only 6.4 months in historical controls. In addition, in patients whose GBM recurred following treatment, the tumors had lost EGFRvIII expression.

"Fast Track status acknowledges CDX-110's potential to fill an unmet need for glioblastoma patients…"

In ACT II, an extension study, a similar patient population was treated with a combination of CDX-110 and chemotherapy. Although the study has not yet reached its median time to progression, preliminary progression-free survival and overall survival rates look similar to those found in the ACTIVATE trial, and as such are highly promising.

Finally, in September 2007, the first patient was randomized to the ACT III Phase II/III study of CDX-110 in combination with radiation therapy and temzolomide in newly diagnosed GBM. The study was designed to investigate the safety, anticancer activity and impact on survival of adding DCX-110 to the standard of care for GBM patients versus the standard of care alone.

"Fast Track status acknowledges CDX-110's potential to fill an unmet need for glioblastoma patients and gives it priority within the FDA," commented Thomas Davis, Chief Medical Officer of Celldex Therapeutics. "Confirmation of the promising results we've already observed is a high priority at Celldex, as it is within the brain cancer community in general."

Source: www.celldextherapeutics.com

AstraZeneca seeks US FDA approval for the use of Seroquel XR™ for bipolar disorder

Drug:	Quetiapine fumarate
Tradename:	Seroquel XR™
Manufacturer:	AstraZeneca
Current indication:	Treatment of schizophrenia in adults
Proposed indication:	Treatment of manic and depressive episodes associated with bipolar disorder

AstraZeneca (NY, USA) recently submitted two separate supplemental New Drug Applications (sNDAs) for the use of Seroquel XR™ in the treatment of manic and depressive episodes associated with bipolar disorder.

Seroquel XR, which is currently approved in eight countries for the treatment of adults with schizophrenia, was reported at the 7th International Forum on Mood and Anxiety Disorders (Budapest, Hungary) in December 2007 to also be effective in the treatment of major depressive disorder and generalized anxiety disorder.

The two sNDA submissions are both based on clinical studies of once daily treatment with Seroquel XR compared with placebo. In the bipolar mania study 316 patients receive Seroquel XR once daily at doses of 400–800 mg/day. The primary end point is a change in baseline Young Mania Rating Scale (YMRS) total score at 3 weeks. In the bipolar depression study 280 patients receive 300 mg/day Seroquel XR once daily with a primary end point of a change from baseline in the Montgomery Asperg Depression Rating Scale (MADRS) total score after 8 weeks.

Both studies have met their primary end points and further results are expected to be presented later in 2008.

Sources: AstraZeneca Press Releases www.astrazeneca.com/pressrelease/5363.aspx; www.astrazeneca.com/pressrelease/5368.aspx.

Positive effect of etanercept on Alzheimer's disease symptoms

Patient experiences rapid improvement in memory following treatment with the arthritis drug

A recent case report, published online on January 9 in the *Journal of Neuroinflammation*, has documented extremely rapid improvements in cognitive abilities in an Alzheimer's disease (AD) sufferer following spinal injection of the arthritis drug, etanercept (trade name Enbrel®).

Etanercept is a TNF-α receptor fusion protein that binds to TNF-α and neutralizes it. Elevated levels of TNF-α are hypothesized to be involved in the pathogenesis of AD. Therefore, researchers investigated the effect of treatment with etanercept on AD symptoms. The study reports the administration of etanercept into the spine of an 81-year old man with early stage AD. Prior to injection a variety of cognitive tests were carried out on the man, who used to be a doctor. Within 10 min following the injection, the man could remember a variety of facts that he had previously been unable to recall, including the year, day of the week and the state in which he lived. He was also much calmer, more attentive and less frustrated following the injection.

Lead author of the study, Edward Tobinick, said the drug had "a very rapid effect that's never been reported in a human being before". He added, "It makes practical changes that are significant and perceptible, making a difference to his daily living."

> "Other experts in the field are also excited about the potential of this novel treatment..."

Sue Griffin, the editor the *Journal of Neuroinflammation* who wrote an accompanying commentary, said "It is unprecedented to see cognitive and behavioral improvement in a patient with established dementia within minutes of therapeutic intervention. This gives all of us in AD research a tremendous new clue about new avenues of research." She added, "Even though this report predominantly discusses a single patient, it is of significant scientific interest because of the potential insight it may give into the processes involved in the brain dysfunction of AD."

Other experts in the field are also excited about the potential of this novel treatment, although they do stress that a great deal more research is required. Rebecca Wood, of the Alzheimer's Research Trust (Cambridge, UK) commented, "This is promising and innovative research, but in the early stages and further work is needed before we can conclude etanercept could work as a treatment for AD. We need to investigate whether it is safe and works in a larger number of patients as well as monitor the long-term effects. Scientists also need to check the benefits weren't just due to the placebo effect and establish whether any benefit is just temporary or whether the disease itself is slowed."

Sources: Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J. Neuroinflammation* 5(1), 2 (2008) (Epub ahead of print).
Griffin WS. Perispinal etanercept: potential as an Alzheimer therapeutic. *J. Neuroinflammation* 5(1), 3 (2008) (Epub ahead of print).