SPECIAL REPORT SUBARTICLE

Hot topics in 2012

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The last year has seen major developments in autism research, such as candidate genes and drug development, as well as some big debates, including the new diagnostic guidelines. Here we explore ten topics that have garnered intense interest.

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1. New approaches to treatment

Normalizing neurons: Treating mouse models of fragile X syndrome (middle) with the drug arbaclofen (right) pares down the number of neuronal projections to normal levels (left).

In one of the most high-profile developments of the year, researchers at **Seaside Therapeutics**, a Massachusetts-based company, announced that a drug called arbaclofen **improves behavioral problems** in people with **fragile X syndrome**. The findings are somewhat controversial because the drug did not meet its primary goal, a decrease in irritability.

Other researchers are studying a variety of approaches in animal models of fragile X, including a **cholesterol-lowering drug called lovastatin**, an **enzyme that regulates protein synthesis**, and an **experimental sleep aid**.

Treatments are showing benefits in mouse models of autism as well, including **an epilepsy drug** in mice with Dravet syndrome, a rare epilepsy disorder, **and bone marrow transplants** in animal models of both autism and Rett syndrome.

Two studies suggest that nutritional supplements may also help treat a small number of autism cases. In one study, researchers found that a **genetic defect in the synthesis of carnitine** slightly increases the risk for autism in some children. In another, an analysis of families with inherited forms of autism showed that rare mutations that **speed up the metabolism of certain amino acids** trigger a potentially treatable form of autism.

2. New candidate genes for autism

Double trouble: Regions of chromosomes that carry an identical genetic sequence from each parent are likely to harbor recessive mutations.

This was a watershed year for autism genetics. The emphasis was on rare variants—those present in less than one percent of the population — and three methods not only firmly identified new risk genes, but also promised to keep delivering them in the coming years.

Sequencing the **exome**, or protein-coding regions of the genome, in people with autism and their families identified a number of new risk genes. Several studies focused on families that have a single child with autism and unaffected siblings, looking for spontaneous, or *de novo,* gene-disrupting point mutations. These studies suggest as many as **500 to 1,000 genes** may be involved in the disorder. Even if scientists identify mutations in these genes in just two or three people with autism, they are statistically highly likely to be *bona fide* risk genes.

Exome sequencing also showed great promise in identifying **causative mutations** present on both gene copies in a number of **families that have multiple members** with autism. Beyond the exome, researchers used next-generation sequencing to identify **balanced chromosomal abnormalities** in autism — chunks of DNA swapped between chromosomes — and found that such events are surprisingly common.

These early results are already providing insights into autism's biology. Estimates from exome data suggest that nearly half of autism risk genes will turn out to be direct **targets of the fragile X mental retardation protein**, FMRP, which should prompt a renewed focus on this critical pathway.

Many genes involved in beta-catenin signaling and **chromatin biology** also seem to be disrupted, pointing to new pathways to explore. Finally, studies identified a number of individuals whose autism may be caused by inborn errors of metabolism, raising the prospect that **dietary supplements** may, in some cases, be effective treatments.

3. Debate over diagnostic guidelines

In December 2012, after years of debate, the American Psychiatric Association approved updates to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The new guidelines, detailed in the forthcoming edition, the DSM-5, include **substantial changes** to the criteria for diagnosis of autism. The guidelines, which the association approved on 1 December, have triggered **intense controversy** in the autism community.

A handful of studies suggested that the new guidelines will exclude some people currently diagnosed with autism, most notably those with milder forms, such as **Asperger syndrome** and pervasive developmental disorder-not otherwise specified. But critics say those studies are based on flawed data, and at least one in-depth study suggested that the **guidelines are unlikely to exclude many**.

4. Artifacts in brain imaging

Wandering thoughts: Several brain areas show high (red) or low (green) activation during subtle changes in emotional arousal, such as when thinking of a loved one.

Arguably the most exciting work in brain imaging in the past couple of years has come from scanning the so-called resting brains of people while they lie passively in the machine.

But this year, several scientists have revealed that the results of some of these studies were due to **participants moving their heads** in the scanner — a particularly common challenge when working with children, and especially children with autism.

Researchers are **working out new techniques** to **limit unwanted movement**, but the artifact has already tainted the scientific record. For instance, it **undermines some of the evidence** used to support the popular 'connectivity theory' of autism, which says that the disorder stems from weak long-range connections.

Even if head motion were not a problem, some researchers are exploring whether the resting brain of a person with autism is **more influenced by emotional arousal** than that of controls.

5. Multiple hits to the genome

Heavy load: Individuals with autism and SHANK2 deletions also carry variations in an autism-linked region of chromosome 15.

In addition to identifying new risk genes, a number of studies published this year support the idea that autism sometimes results from more than one hit to the genome. This may help explain why certain genetic variations seem to have variable outcomes, ranging from autism to mild intellectual disability, schizophrenia or general developmental delay.

A large-scale study of more than 2,700 children with **copy number variations** (CNVs) — deletions or duplications of DNA — found that those with developmental delay are **eight times more likely** to have two CNVs than controls are.

A study of the autism-linked gene **SHANK2** found that three people with autism have **mutations in that gene** as well as a CNV in an autism-linked region of chromosome 15.

And a third study found that common genetic variants — which are found in five percent or more of the population — **together contribute significant autism risk**. (Large studies of common variants have failed to reliably identify individual variants that carry significant risk.)

6. Neurodevelopmental disorders in the adult brain

Strange synapses: Mice lacking NLGN3 develop abnormal neuronal connections (yellow) at one end of certain cells (blue) in the cerebellum.

Autism is a disorder that begins early in life, perhaps even in the womb. But several mouse studies published this year show that some autism-linked proteins play crucial roles in the adult brain. They add to a growing body of research in animal models suggesting that the neural deficits associated with autism-like disorders can be treated into adulthood. If the findings hold true in people, it would extend the window for treatment.

Two studies suggested that the brain may be able to be rewired to some extent after the critical period of infant development. Restoring production of the autism-linked protein neuroligin-3 in young mice **reverses abnormalities in their neurons**, and giving adolescent mice **a drug that**

has shown promise in the autism-related disorder **fragile X syndrome** improves sensory sensitivities and problems with learning and memory.

Another study bolstered the view that the protein involved in another autism-related disorder, Rett syndrome, is **vital to the functioning of the adult brain**. The study suggested that treatments targeting this protein would have to be given throughout a person's life.

7. Insight from baby sibs

Click to enlarge image Mouth mismatch: An eye tracking study shows that infants at high risk for autism have trouble detecting when a video doesn't match its audio track.

So-called '**baby sibs**,' the younger siblings of children with autism, have up to a 20-fold increased risk of developing the disorder. A number of baby sib studies yielded intriguing results in 2012, including the first hints of characteristics that may predict which children will go on to develop autism.

In February, investigators from the **British Autism Study of Infant Siblings** network reported the first evidence of brain activity that might predict later development of autism. They found that baby sibs who go on to develop autism **have a different brain response to gaze** than those who do not.

Results from the **Infant Brain Imaging Study** in the U.S., published later that month, show that baby sibs who go on to develop autism **have abnormalities in white matter**, the bundles of nerve fibers that connect different regions of the brain, as early as 6 months of age.

Other studies published this year found that baby sibs have more difficulty integrating **information from their vision and hearing**, and **low brain activity** across many different frequencies. Their brains also **don't distinguish between** scrambled motion and biological motion, or the movement of bodies, the way controls do.

8. Brain's chief executive

Cognitive control: People with autism can do well on tests measuring executive function skills — if those tests, like this challenge to remove a cork from a tall glass cylinder, don't require them to

infer what an experimenter is thinking.

The autism literature is rife with mixed results of cognitive testing in people with autism. For example, some studies suggest deficits in flexible thinking or in carrying out multi-step tasks, but others do not. Researchers are starting to better resolve these inconsistencies by designing sophisticated tests that detect exactly why people with autism struggle with these skills in the real world.

In May, a provocative paper suggested that people with autism do poorly on some tests of executive function, a set of complex mental processes involved in planning, organizing and similar activities, because they have **difficulty imagining what other people are thinking**.

Later, a review marshaled evidence from more than three dozen studies to show that people with autism **don't spontaneously pay attention** to social information, even though some can correctly interpret such information if specifically asked to do so in a laboratory test.

Finally, a new computer-based test debuted at the **Society for Neuroscience annual meeting** in New Orleans showed promise for capturing the **difficulties people with autism have in flexible thinking**.

9. The downside to data hoarding

The Jackson Laboratory Public progress: Once results from a new mouse model are published, scientists may send the animals to The Jackson Laboratory, a nonprofit repository.

Sharing data has always been a tenet of the scientific enterprise, but in today's world of über-competitive research funding, it's becoming increasingly more difficult to do. This year, the autism community began to talk more openly about the benefits of sharing data.

Some researchers have **chosen not to send** their mouse models of autism to a central repository — even after the models have been published. Critics say this slows progress because other researchers can't study them in more depth. In fact, in order to make one particularly hot mouse model available to the research community, a small nonprofit opted to **fund to recreate the mouse**.

Generosity benefits the sharer, too. It can act as insurance against unanticipated damage to a single lab, as New York University researchers learned in October **after Hurricane Sandy struck**. Pooling data can also increase statistical power, which is **particularly helpful in genetic studies**.

10. Growing role for the immune system

Heating up: Julius Wagner-Jauregg treated several men with psychosis by exposing them to malaria, and won a Nobel Prize for the work.

For more than a century, researchers have found intriguing links between the **immune system and psychiatric disorders**. Several groups are reporting biological mechanisms linking immune function to autism.

One study, for example, found that children with autism have **abnormal blood levels of immune molecules** called cytokines at birth. Several other papers found that microglia — the brain's immune soldiers — are **important for brain development**, and show up in **abnormal clusters** in the brains of people with autism.

And perhaps most provocatively, researchers have reversed symptoms in both a **genetic** and an **environmental** mouse model of autism by wiping out the animals' immune systems with a bone marrow transplant.