SPECIAL REPORT SUBARTICLE

Hot topics in 2013

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This year saw the emergence of a few unexpected twists in autism research, and provided fresh insights into some of the usual suspects. Based on suggestions from several researchers and SFARI staff, here's our list of the top ten topics this year.

1. Broad spectrum of neurodevelopmental disorders:

Seeking significance: A new statistical analysis can help determine whether a mutation in a person with autism is related to the disorder.

Autism often occurs in combination with other brain disorders, such as **epilepsy**, intellectual disability and schizophrenia. A number of studies this year contributed to the concept of **these disorders being on a continuum**, with common underlying genetics.

For example, as researchers reported in August, children with autism are **more likely to have epilepsy** if they also have intellectual disability. Researchers also identified genetic links between **autism and childhood-onset schizophrenia**, and between autism and a brain malformation called **agenesis of the corpus callosum**.

One group documented small *de novo*, or spontaneous, mutations in multiple individuals with **autism, epilepsy or intellectual disability**. Other researchers also showed that de novo **mutations found in individuals with epilepsy** overlap with those seen in autism. They also found that *de novo* mutations are more common in people who have **both autism and intellectual disability**.

Inherited mutations **also contribute to the co-occurrence** of autism and intellectual disability. These mounting links have led some researchers to argue that, especially for research purposes, the disorders should be studied together under the broad umbrella of '**developmental brain dysfunction**.'

2. Is head size a true autism marker?

Heady bias: Studies that rely on dataset norms are more likely to report large heads in children with autism than are those that locally recruit controls.

Large head size has been considered a feature of autism since Leo Kanner **first described the disorder** in the 1940s. However, several studies this year caused researchers to take a closer look.

Perhaps the most shocking piece of news came from a meta-analysis published in June, which found that most studies evaluating head size use biased control samples and may have **overestimated the head-size effect** in children with autism. Another study found that children with autism have on average only slightly larger heads than their unaffected siblings.

However, a study of twin pairs reported that both **children with autism and their unaffected twins** have larger heads than average. The results suggest that whatever factors lead to enlarged heads are not sufficient to cause autism on their own.

Findings from other studies published this year indicate that head size is a clear example of autism's heterogeneity. For example, a study in March found that children with autism whose heads and bodies are both larger than average **have different symptoms** than those who have enlarged heads alone. Another study reported that the brains of children with autism whose mothers carry certain immune molecules are **12 percent larger than** those of controls.

Two other studies found **differences between the sexes**: Girls with autism often have small heads and bodies compared with controls, whereas boys have average-sized heads and slightly larger bodies.

3. Gender differences in autism get their due:

Measuring up: Only male toddlers with autism may be larger overall than typically developing controls.

It's still a mystery why autism is four times more common in boys than in girls, but several studies this year provided insight into how the disorder varies between the sexes.

The topic took center stage at the **2013 International Meeting for Autism Research** in San Sebastián, Spain, in May. Girls with the disorder **carry more mutations** than boys, reported a study from **Matthew State's** lab at Yale University, suggesting that girls are protected from autism and need more genetic hits to develop the disorder.

A February study of 10,000 pairs of fraternal twins supported the theory that girls have a **baseline level of protection** against autism. Twin siblings of girls who have many autism traits show more autism symptoms than do twin siblings of boys with many autism traits. This suggests that girls are more likely to have autism-like behaviors in families with a history of the disorder, but boys can have these traits even in low-risk families.

Young girls with autism are more likely to have **smaller heads and bodies** than controls, but boys with the disorder tend to have average-sized heads and slightly large bodies, according to two studies published in July. It's possible that the small head size is a sign of more severe brain dysfunction in girls, the researchers say.

According to a report presented at the **Society for Neuroscience annual meeting** in November, men and women use **different neural pathways** to recognize faces, a finding that may help autism researchers study **face-processing deficits** in people with autism.

4. Long look at genes reveals surprise links to enzymes:

Long game: Autism-linked genes are 217 kilobases on average, compared with 59 kilobases for a typical gene expressed in neurons of the cortex.

In a surprising twist (or untwist, as it were), two studies this year discovered links between autism and enzymes called topoisomerases that unwind tangles in DNA. One study, published in September, found that topoisomerases are **crucial for the expression** of particularly long genes.

At the same time, the researchers made the surprising discovery that genes linked to autism are four times longer on average than all other genes expressed in neurons. The paper suggests that disrupting topoisomerases would have a preferentially strong effect on autism genes, suggesting new avenues for drug treatment.

In the same month, two other groups of researchers published **their converging findings** that a certain topoisomerase (which surprisingly may uncoil RNA instead of DNA) may be linked to both schizophrenia and **fragile X syndrome** — implicating topoisomerases even more deeply in neurodevelopmental disorders.

5. Early indicators of autism:

Head size: Some children with autism (bottom) have both enlarged heads and an excess of brain fluid.

Children who begin behavioral therapy early in childhood have the best chances of **improving their autism symptoms**, making early identification of utmost importance. A groundbreaking November study provided one clue: Infants who are later diagnosed with autism **lose interest in other people's eyes** between 2 and 6 months of age. This the earliest reported marker of autism to date.

There are other early indicators that a child is at high risk of autism. Infants later diagnosed with the disorder have **excess fluid** between the top of the brain and the skull from about 6 months to 2 years of age, according to a July study. Even *in utero*, the placentas of children who are at high risk of autism may be more likely to have **abnormal folds**.

Brain activity tests may predict autism severity. When listening to familiar and unfamiliar words, high-functioning 2-year-olds later diagnosed with autism show a **brain response** that is similar to that of controls. They also perform better on tests of cognitive ability, adaptive behavior and receptive language at 4 and 6 years of age compared with lower-functioning children with autism.

6. Brain’s garbage collectors get fresh look:

Missing myelin: When the developing rat brain loses microglia (green, right), it causes a dramatic loss of myelin (red), the fatty substance that insulates neuronal branches.

For many decades, brain cells called microglia were thought to be the brain's garbage collectors, ingesting pathogens, misfolded proteins and other cellular debris. In the past few years, however, **the cells have proven to be multi-taskers**, involved in many processes, including the development of **synapses**, the junctions between neurons.

Postmortem studies have shown that microglia are **altered in the brains of people with autism**, but it's unclear whether this is a cause or consequence of the disorder. A new technique may help clarify that relationship. Early in 2013, researchers from Japan debuted a **method to detect microglia** in the brains of living people, using a brain imaging technique called positron emission tomography. Microglia changes across development might one day be used to signal autism risk, the researchers say.

Other insights about microglia came up at this year's **Society for Neuroscience annual meeting** in November. Researchers showed that in newborn rats, **microglia are crucial for the production of myelin**, the fatty substance that wraps around nerves and quickens the transmission of electrical messages. What's more, this myelin connection may help explain the reported **link between autism and prenatal exposure to antidepressants**.

7. Editing genomes, one mutation at a time:

Cut and paste: Genome-editing proteins generally have one part that binds a DNA sequence and another that snips out that code.

For years now, researchers have been able to take skin cells from people with certain disorders, such as autism, and use chemicals to reprogram them into neurons. **Despite the popularity of this approach**, it has a few downsides. One is that because each person carries many genetic variants — some damaging, some benign — it is difficult to pin down which ones are responsible for any particular change in the cell.

Genome editing, in contrast, allows scientists to investigate one or several genetic mutations in a precisely controlled way. For example, this year, researchers debuted a technique called CRISPR, which allows them to cut and paste essentially any mutation into the genome of any cell, including a human stem cell. Several groups are **using CRISPR and similar technologies to model autism-related disorders** such as Rett and **Angelman syndromes**. These tools, once the stuff of

science fiction, are getting cheaper and more accessible by the day. At the **Society for Neuroscience annual meeting** in November, for example, one group **described a free software** program to help others design their own customized molecular scissors.

8. Too much of a good thing:

Troubled translation: A mutation that triggers excess protein production at the connections between neurons also leads to abnormal social behavior.

This year, new findings continued to bolster the idea, **highlighted in a 2012 study**, that autism may be linked to an overload of proteins in the cell. Several autism-related disorders, such as **fragile X syndrome**, have long been known to **boost protein production**: FMRP, the protein missing in fragile X, normally slows down this process. A study published in February reported that a protein found in excess in some people with autism is **a key player in the protein-making machinery**. This protein is involved in the **PTEN** and **mTOR** pathways — both of which are linked to autism — and may boost production of neuroligins, **key players in autism**.

9. For sale: Genetic tests, with a side of caution:

Each passing year brings more genetic tests for autism — and more controversy over the accuracy of the tests. This year began with an intriguing survey from a French company, **IntegraGen**, which **had begun selling a $2,895 test** for autism. The company claimed that the test could accurately estimate the risk of autism in **younger siblings of children with the disorder**. The survey found that **80 percent of parents** who have a child with autism would use such a test.

In May, another company, **SynapDx**, launched a clinical trial of a blood test that looks at changes in the expression of genes. A study sponsored by the company had previously claimed that a panel of 55 genes **can predict autism in boys** with 73 percent accuracy. The clinical trial, which aims to recruit 660 children, plans to **investigate the test's ability** to distinguish autism from related disorders.

Scientists are rightfully cautious about these claims because genetic tests that look effective in early studies are often later discredited later. Case in point: In October, researchers said that a genetic test based on 237 markers, and developed by an Australian group in 2012, **does not accurately predict autism**. The Australian group's findings may have been tainted by differing

ethnicities between the autism and control groups.

10. Balancing signals of excitation and inhibition:

Stretching out: A drug can reverse (right) the abnormal curled-up posture seen in mice that model Angelman syndrome (center). Control mice are shown on the left.

One popular theory for what causes autism proposes that the disorder is a **consequence of an imbalance** between excitatory and inhibitory nerve signals in the brain.

In June, a mouse study found that a mutation that causes tuberous sclerosis complex, an autism-related disorder, may **dampen inhibitory signals in the brain**, resulting in too much excitation. Researchers also found evidence in mice that decreased inhibitory signals in the cerebellum may cause the **motor problems seen in Angelman syndrome**, another autism-linked genetic disorder.

Meanwhile, **rats exposed *in utero* to valproic acid**, which show social deficits reminiscent of autism, have higher levels of a protein involved in sending excitatory signals, and lower levels of an inhibitory signaling protein, compared with controls.

Studies in people with autism-related disorders support this theory as well. An analysis of postmortem brains revealed in March that deletion of the 22q11.2 chromosomal region **shifts the location of neurons** that inhibit brain signals. And an imaging study published in July showed that children with autism have **low levels of gamma-aminobutyric acid,** an inhibitory signaling molecule.