Special Series: Autism's new frontiers

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Linda Murphy and her 19-year-old daughter, Ashley Corbett, who has severe autism. Linda is concerned about finding support services as her daughter... more

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BY PAULINE TAM, OTTAWA CITIZEN FEBRUARY 17, 2013

OTTAWA — Even with a diagnosis of autism, Mica Jovanovic remains a medical mystery to experts who treat and study his condition.

And as autism has emerged as the fastest growing developmental disability, stirring fears of an epidemic, researchers are racing to figure out what causes the condition and why it appears to be affecting so many more children.

What's clear is that as a baby growing up in suburban Ottawa, Mica was often sick. By his second birthday, he had suffered 17 ear infections and been treated with countless rounds of antibiotics. The fluid buildup in his

ears impaired little Mica's hearing. He also had swollen adenoid glands, which affected his ability to breathe and sleep normally.

In the first two years of her son's life, Anne Jovanovic made sure her son slept in the crook of her arm so that his head was elevated and he could breathe. Despite her best efforts, mother and Mica slept fitfully.

Other problems emerged after Mica had adenoid and tonsil surgery. While his breathing, sleeping and hearing improved, his parents noticed their son seemed lost in his own world. He rarely made eye contact and tuned out anyone who called his name. He was fascinated by objects, such as spoons, which he held at a distance and examined from all angles.

He cried all day long at daycare, especially when his routines were interrupted. Crowds, loud noises and busy places, such as shopping malls, triggered meltdowns.

"He would be completely inconsolable," his mother recalls. "He would be on the floor howling like a wounded kitten."

Most worrisome for his parents was Mica's inability to communicate. What few words he spoke were not used to express his wants or needs. It wasn't even clear that words had any meaning for Mica, pronounced Mee-cha. At times, he seemed to treat his parents like inanimate objects, neither greeting them nor acknowledging them.

"He certainly didn't call me 'mummy' or his father 'tata,'" recalls Anne. "But he would walk around the room and things that he recognized, he would label: window, door. He would just walk around the room doing that. And that would be the only type of language that he would use."

At three, Mica was diagnosed with a severe form of autism spectrum disorder, which affects many aspects of his development: intelligence, perception, socializing skills, language and emotion.

Now five, Mica's tantrums have subsided and he has shown bursts of improvement in understanding language, thanks to intensive speech and behavioural therapy. He delights in counting from one to 20 and singing, "I'm a Little Teapot," a favourite song. With his sharp memory, he can recite monologues, name objects and echo what others say.

Yet despite learning to use two- or three-word phrases to convey what he wants, Mica still can't carry on a normal conversation. When he's anxious or excited, he will flap his wrists, rotate them, or wring them in front of his face, covering his big brown eyes. Getting his attention, and holding it, continue to be a challenge.

Because no one can pinpoint the exact causes of Mica's autism, treatment is imprecise. And to the dismay of Mica's parents, doctors continue to dismiss the physical symptoms — sleeplessness, frequent illnesses, digestive and immune problems — that often accompany autism's core features, instead of recognizing them as potential clues to what the underlying problems might be.

Officially, autism remains a developmental disorder that psychiatry defines by what people on the spectrum are unable to do: socialize, communicate, follow instructions, grasp abstract ideas. Accompanying these deficits are unusual behaviours that include obsession with routine and repetition, motor problems, hyperactivity, seizures — all of which are believed to stem from variations in early brain development.

However, the conventional definition of autism is being challenged as scientists learn more about the genes, cells, antibodies, brain circuitry and metabolism of people on the spectrum.

As the pace of discovery has picked up, it has become clear that in a vast majority of cases, autism is not caused by a single factor. Instead, it is the result of complex combinations of genetic and environmental factors that are hard to tease apart. Genes matter, but researchers can't tell how; environmental conditions matter,

but they are not sure which.

Some experts now say that while autism certainly involves the brain, it is actually a collection of problems that affects the whole body, from molecules to cells to organs. Also impacted are the immune and digestive systems, leading to health problems that doctors often overlook.

A **U.S. study** looking at the health records of more than 14,000 people with autism shows that they are more likely than the general population to suffer from a number of conditions. They include: anxiety or depression (60 per cent); epilepsy (20 per cent); schizophrenia (two per cent); general gut complaints (12 per cent); and inflammatory bowel disease, Type 1 diabetes or immune-related disorders (one per cent).

Rather than being hardwired into a person's genes, some experts say, autism is the result of an accumulation of seemingly minor events that starts in the womb: perhaps a genetic mutation, some toxic exposures, a stressful birth, a vitamin deficiency, a series of infections, poor diet.

"Now we're realizing that while genes create vulnerabilities, things in the environment, including what we eat and what products we use, make things a whole lot worse," says Dr. Martha Herbert, a pediatric neurologist at Harvard Medical School and Massachusetts General Hospital.

At some point, these problems pile up to form the catch-all condition known as autism, with each person having a unique set of symptoms that vary in severity and could change over a lifetime.

Some people with autism don't speak at all, while others are fluent. Some are bothered by loud noises; others are musical prodigies. Some are intellectually delayed, others highly intelligent. Many people on the spectrum have trouble making friends and participating in the world. A large number develop anxiety and

depression on top of autism.

As the condition continues to be diagnosed more frequently, debate is intensifying over whether there is an actual increase. The U.S. Centers for Disease Control and Prevention **estimates** that one in 88 children now has some form of autism — 20 times the prevailing figure in the 1980s. The most up-to-date Canadian **estimate** suggests one in 94 children has the condition.

Some researchers maintain the steep rise has more to do with a surge in diagnosis than in real disease. They say factors that have nothing to do with biology — an expanded definition of autism, greater awareness of the disorder, an improved ability to distinguish it from other conditions — are fuelling the boom. Others suspect something in the environment is causing a terrible epidemic.

However, because no two people have the same combination of autistic features, scientists find it difficult to uncover what causes the syndrome in all its forms and how it develops. Researchers say identifying what has gone awry would improve diagnosis and point the way to new targeted treatments. It would also reveal what, if anything, could be done to prevent autism.

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As recently as a few decades ago, psychiatrists thought autism was caused by bad parenting. And while that notion has been discarded in favour of genetic explanations, there has been growing acceptance that genes do not tell the whole story. That's in part because even with more frequent diagnoses, autism rates are increasing far faster than genes evolve.

"There is something going on and there's a good chance that environment plays some role in that," says Irva Hertz-Picciotto, an epidemiologist at the University of California Davis MIND Institute, a leading autism research centre. "Genetics don't change that much in two or three decades."

Studies of twins have long supported the importance of genes in autism given that the condition tends to run in families. Other **studies** confirm that a family with one child on the spectrum is many times more likely to have a second with the diagnosis. Likewise, identical twins, who share the same genetic code, are more likely to share a diagnosis than fraternal twins.

However, recent research has shown that even among identical twins, the condition could occur in one but not the other, hinting that something outside a child's DNA could trigger the disorder. The largest study of twins, published in 2011, suggests that environmental factors, such as conditions in the womb and early childhood, are at least as important as genes in causing autism. The **study**, led by Stanford University psychiatrist Dr. Joachim Hallmayer, is part of a general shift in how autism is being discussed.

To date, scientists searching for a lone genetic culprit have come up empty. With the exception of a few rare disorders, such as Fragile X or Rett Syndrome, which can lead to forms of autism, no recurrent single gene, or common set of genes, has been shown to cause all types of autism. That means there is no autism gene anywhere near common enough for a simple screening test to be developed for all newborns.

Rather, there could be **hundreds** of genetic glitches that can cause autism, says geneticist Stephen Scherer, who runs the Centre for Applied Genomics, Canada's first human-genome laboratory, at Toronto's Hospital for Sick Children.

"In some cases, it's going to be a single gene involved and in other cases it's going to be combinations of genes, both scenarios of which necessitate scanning the entire human genome to get the diagnosis correct," he says.

Taken together, the genetic changes identified so far account for up to **20 per cent** of all autism cases. And with powerful new tools that allow scientists to analyze a person's complete

genetic makeup, more discoveries are on the way. Scherer, who is part of an international team working to decipher the genetic codes of 10,000 families with autism, says the research is moving so quickly that within five years, researchers will have identified all the genes involved.

Ultimately, those genes could explain up to 90 per cent of all autism cases, says Scherer. “We anticipate that this number will increase as we use higher resolution technologies that allow us to scan the DNA.”

To date, Scherer’s lab has analyzed the genomes of 1,600 families and uncovered some of the glitches linked to autism. In one **study**, Scherer has found that DNA changes along specific regions of the genome known to be involved in brain development raise a person’s risk of developing the condition. However, like previous studies that have produced a scattering of gene findings, Scherer’s results account for only a fraction of all autism cases.

Another **study** shows that the loss or duplication of a gene — having one or three copies of a particular gene instead of the usual two — is also a risk factor. This is especially true of genes that play a major role in determining how nerve cells in the brain communicate.

When it was published in 2008, Scherer’s study of these repetitions and deletions in the genetic code, known as copy number variations, was hailed as an important discovery because it was part of a growing body of research that upended the long-held assumption that everyone inherited two copies of every gene, one from each parent.

And while some of the genetic risk factors for autism are, indeed, passed down from a parent, emerging **research** suggests certain DNA changes don’t always have a clear family pedigree. Instead, some of the random genetic changes that are found in children, but not their parents, probably occur at conception, when

DNA is most likely to be lost or duplicated.

Most people have these spontaneous changes, known as de novo mutations, and the majority of them are harmless. But if they happen to land in a particular part of the genome that is critical to early development, autism can result.

Increasingly, researchers suspect that environmental conditions — from the air you breathe to the food you eat — conspire with genetic vulnerabilities to influence de novo mutations.

“Something is causing these mutations, and we really need to consider that environment could be playing a major role in creating them,” says Herbert, the Harvard neurologist and author of **The Autism Revolution**, a book which argues that the condition is a whole-body disorder.

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At the UC Davis MIND Institute, Hertz-Picciotto, the epidemiologist, has spent the past decade uncovering clues about conditions that could trigger autism. Early signs points to factors that influence a woman’s health before and during pregnancy: **poor nutrition**; bacterial and **viral infections**; and exposure to high levels of **air pollution** and **pesticides**.

Obesity, hypertension and **diabetes** have also been implicated as risk factors, suggesting that at least part of the rise in autism could be tracking a global epidemic of inflammatory diseases.

Yet because Hertz-Picciotto’s studies don’t prove cause and effect, merely links between certain factors and autism, the investigation continues. Hertz-Picciotto suspects it’s not only the combination of factors, but also the timing of those events at critical stages of early development that set the stage for autism.

And as the nature-versus-nurture debate rages on, scientists are realizing that genes don’t actually have to be mutated in order to act differently and trigger autism.

Under certain environmental conditions, genes stay the same, but their on-and-off signalling switches change, with some slowing or shutting down, and others kicking into overdrive. These “epigenetic” changes, which accumulate over a lifetime and can arise from things like a mother’s diet and stress levels, can influence gene function in a child without ever tampering with the structure of a gene itself.

One example of epigenetic change comes from a **study** by Hertz-Picciotto and her collaborators that shows women who don’t take prenatal vitamins in the months before they get pregnant increase their child’s risk for autism.

This is especially true for women who have genetic mutations that make it difficult for them to convert folic acid, a key ingredient in prenatal vitamins, into a chemical that’s essential for fetal development. “This is perhaps the very first concrete example of gene-environment interaction,” says Hertz-Picciotto.

Other researchers are using the gene-environment approach to explore the possibility that at least a subset of autism could be a type of inflammatory disease. Hertz-Picciotto’s colleagues at the MIND Institute, led by immunologist Judy Van de Water, are investigating potential ways that the brain and immune system work hand-in-hand to make the body more vulnerable to autism. Van de Water’s team has shown that the two **systems**, rather than operating independently, actually talk to each other as part of a continuous feedback loop and are particularly sensitive to environmental changes.

The theory, based on **studies** suggesting that some children on the spectrum have faulty immune systems, adds weight to the idea that autism is a whole-body condition.

“At least in some cases, it’s not solely a neural disease, it’s not an immune-mediated disease, it’s the neuro-immune interaction that we’re investigating,” says Van de Water.

Her team has found that a number of mothers

whose children go on to develop autism show signs of immune problems during pregnancy. One **study** identifies rare antibodies in the mother's blood that bind to fetal brain cells, potentially disrupting healthy brain development. While it's not clear why some women produce these antibodies and others don't, Van de Water provides some clues in another **study**. Her team shows that mothers carrying certain autism risk genes run an abnormally high risk of producing these autism-linked autoantibodies.

Van de Water says pregnant women who carry these autism risk genes could be primed for an overactive immune response if, for example, they catch an infection such as flu. That over-activation — the result of an immune response that doesn't know when to quit — can lead to chronic inflammation and change, not only the fetus's brain development, but also the baseline settings of its immune system, making it more vulnerable to autism.

"That's one way that autism could be an immune-mediated disorder because the maternal immune system is changing the way the fetal brain develops," says Van de Water.

Likewise, parents with an autoimmune disease — such as diabetes, rheumatoid arthritis, or celiac — run a higher-than-average risk of having a child with autism. However, it remains unclear whether immune problems on their own are enough to cause autism, and if not, how many other genetic vulnerabilities or environmental triggers need to accumulate to push a child toward the condition.

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