

CANADIAN ECD RESEARCH IN 2004

IS THERE A WORLD BEYOND GENETICS?

by Richard E. Tremblay, CEECD Director

In 1968, one of my graduate school professors recommended a book entitled "Beyond reductionism: New perspectives in the life sciences."¹ The book was published to counterbalance a "narrow biological view of human behaviour" that had "invaded" the life sciences. Molecular genetics was a major culprit, and the founder of a famous department of genetics, the embryologist C.H. Waddington, was now trying to convince his colleagues that there was a world beyond molecular genetics.

He was far from successful. He died in 1975, and molecular genetics flourished. If you haven't noticed how genetics has invaded ECD, a glance at this fourth instalment of the CEECD's Top Ten papers by Canadian investigators should convince you. Fully half of the papers include some form of genetic analysis.

Genes are the fashion of the day. But pay special attention to the study on early care (page 4) and to our featured investigator (page 2). Waddington's dream is finally com-

ing of age. He coined the word "epigenetics," which Michael Meaney and Moshe Szyf use to describe their amazing discovery that genes are turned on, or not, by the amount of licking a rat pup receives from its mother. The licking is transformed into a chemical signal that actually tells the genes to speak their mind. After "genetic programming," we are now into "environmental programming."

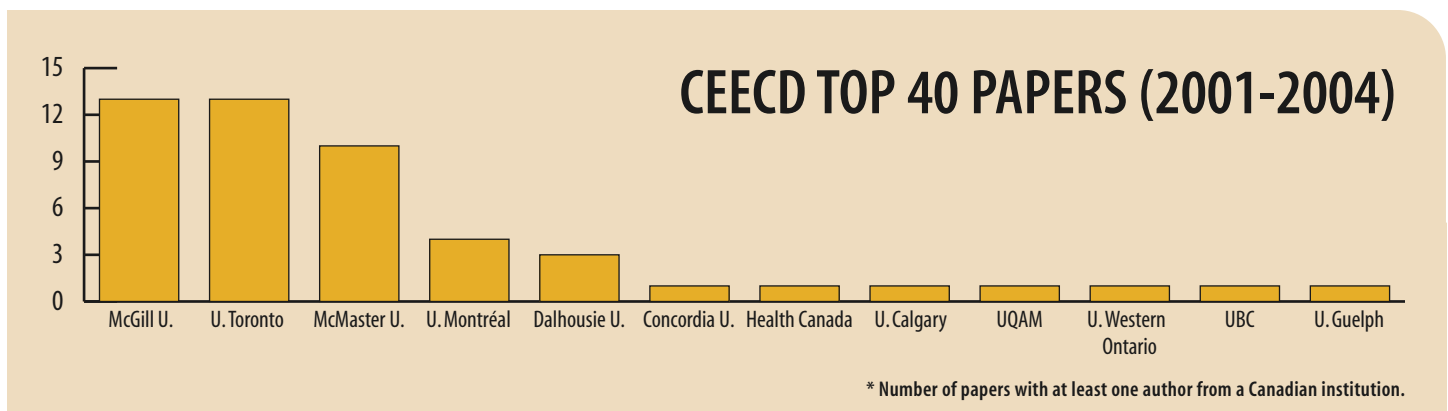
Our featured Canadian investigator, Michael Meaney, started his career studying

social behaviour in rats, including play-fighting. He went on to study the long-term effects of early maternal behaviour on the stress response. Four of his papers have made the CEECD Top Ten in the last four years. His work even caught the eye of the Dalai Lama who invited him to discuss his findings. An invitation to receive the ultimate prize from the hands of the king of Sweden in Stockholm on an early December day would not be surprising.

Our yearly Top Ten round-up of scientific papers has now produced 40 papers. At least one author of each paper is from a Canadian research institution. The figure at the bottom of the page shows the distribution of authors among Canadian research institutions. For example, McGill and the University of Toronto each had at least one author on 13 of the 40 articles, while McMaster had at least 10.

The Canadian investigators who will produce the next generation of top papers on early childhood development will most certainly have to take C.H. Waddington's recommendation seriously: to understand development, we must take into account both genes and environment. ¶

¹Koestler A, Smythies JR. *Beyond reductionism: new perspectives in the life sciences [proceedings of] the Alpbach Symposium 1968*. London, England: Hutchinson; 1969.



DR. MICHAEL MEANEY: MORE CUDDLES LESS STRESS!

by Liz Warwick

As a young undergraduate, Michael Meaney was wavering between biology and psychology. Then he came across studies showing that stimulation in early infancy could alter stress responses in rats. "I was immediately taken with the question of how such effects occurred and how they persisted over the lifetime of the animal," he says.

The James McGill Professor of McGill University's Departments of Psychiatry and Neurology and Neurosurgery has a special interest in maternal care and how differences in such care can modify an individual's brain development and the ability to deal with stress later in life.

MOM'S ACTIONS MODIFY DNA

Many of his recent experiments have focused on animals—often rats—who show either high or low levels of nurturing care through licking and grooming their offspring. By studying the offspring who received different levels of care, Meaney and his colleagues have made a startling discovery: the kind of care a mother gives to her offspring alters the chemistry of the DNA in certain genes involved in stress response. Animals who received a great deal of licking and grooming produced fewer stress hormones when dealing with a challenging or stressful situation than the rats who received less care. The effects continued into adulthood, an important point given that stress hormones have long-term effects on the body. When too many of these hormones are produced over a long period of time, there is an increased risk for chronic problems such as heart diseases and diabetes.

Meaney's work with animals suggests that security is key to healthy outcomes for



DR. MICHAEL MEANEY

kids. "Secure offspring, regardless of the species, secrete higher levels of growth-promoting hormones and lower levels of stress hormones. The issue then is the nature of the behaviours that favour security in children." To find out more about these behaviours—and the situations that favour or work against them—Meaney is now doing a significant part of his research with human mothers and children.

HELPING PARENTS COPE WITH STRESS

However, whether his research subjects are humans or animals, Meaney says the implications of the work he has been doing are clear, and suggest a profound need for policies and practices that support families and children, especially in the early years. "Women's health is critical," he says. "The single most important factor determining the

"The single most important factor determining the quality of mother-offspring interactions is the mental and physical health of the mother"

quality of mother-offspring interactions is the mental and physical health of the mother. This is equally true for rats, monkeys and humans."

However, policy-makers must keep in mind that parental behaviour, like any other behaviour, is determined by environmental conditions. So parents living in poverty, suffering from mental illness or facing great stress are much more likely to be fatigued, irritable and anxious. "These states clearly compromise the interactions between parents and their children," he says.

Finally, he adds that people tend to get too involved in pointing out differences between humans and other species. "The fundamental message for public policy is that the health of the mother will determine the development and health of the offspring. In fact, this is no less true for insects than for humans." 🦋

OVERLY STRESSED?

MAYBE IT WAS YOUR CHILDHOOD!

by Liz Warwick

Few people can escape the pressures of the modern world, but some seem to respond better than others to the stresses that surround us. Researchers have started to examine how humans respond to stress and why people react in different ways. A team of Canadian scientists have found a link between people's responses to stress and the care they received in their early years.



The researchers selected two groups of adults ages 18 to 30. One group had reported receiving high levels of care during childhood, while the other reported low levels of care. Participants were then put into a stressful situation. They were asked to complete a series of mathematical tasks while being told they were making mistakes and needed to improve. During this stress task, researchers used a PET, or positron emission tomography scan, to measure the levels of a chemical called dopamine in a particular area of the brain (the ventral striatum). In animal studies, dopamine has been shown to be released during stress. The researchers also measured levels of cortisol, the so-called stress hormone.

LESS CARE, MORE STRESS

For the first time in a study with humans, researchers found that dopamine was released during stressful situations. However, they also found that dopamine and cortisol levels were higher in the group who had reported receiving low levels of childhood care. This group had a stronger physical reaction to the stress, as measured by chemical activity in the brain. Michael Meaney, one of the study's researchers, notes that the findings are consistent with past animal

studies showing that early maternal care can directly alter the development of the brain's stress regulatory systems.

Dr. John C. LeBlanc, Assistant Professor of Pediatrics, Psychiatry, Community Health and Epidemiology at Dalhousie University, calls the findings "provocative." They suggest that "the type of parenting that we were exposed to has a permanent impact on how we respond to stressful situations and that this can be measured in terms of physical brain activity. However, the study falls short of proving a cause-and-effect relationship because of the small number of subjects and because parenting style itself was determined to some extent by the temperament of the research subjects when they were young children," he notes. Nevertheless, Dr. LeBlanc says, "this finding implies that we need to research thoroughly the long-term impact of parenting on brain function so that we can better understand how to promote optimal brain development."

The study's findings suggest that early interventions, especially with children "at risk" for less than optimal care, could have positive and long-term benefits, according to George M. Tarabulsky, a professor in the

"Early maternal care can directly alter the development of the brain's stress regulatory systems"

École de psychologie at the Université Laval. "Children who grow up in high-risk circumstances more often struggle with important developmental problems linked to both internalization and externalization behaviour problems throughout the life span," says Tarabulsky. "Consequently, these children are (again, throughout the life span) over-represented in all facets of services provided by society and at great human and economic cost."

Early intervention programs aimed at improving parenting skills and enhancing the parent-child bond, could provide a way to offset the potential harm. "With quality prevention in high-risk contexts, infant and early child brain development may be enhanced," says Tarabulsky, ultimately leading to better cognitive, social and emotional development in young children. 🦋

Ref.: Pruessner JC, Champagne F, Meaney MJ, Dagher A. Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [C-11] Raclopride. *Journal of Neuroscience* 2004;24(11):2825-2831.

EARLY CARE PROGRAMS CERTAIN KINDS OF GENES

by Liz Warwick

Care received in the very early years is literally written into the body, a new study suggests. Previous research has shown that rats receiving a great deal of maternal care (licking, grooming, nursing) in the first few days of life are less fearful and produce fewer stress hormones.

However, in a new study, researchers examined actual epigenetic differences in the brains of rats born to mothers who were more or less nurturing. Depending on the care received, the rats had differing levels of DNA methylation (a chemical change that affects how a gene will be expressed) in a key area of the hippocampus. The differences in DNA methylation lasted into adulthood and had an impact on how the offspring responded to stress. Differences could also be induced by a process called cross-fostering in which rats born to mothers providing low levels of care are put with mothers providing high levels of care (and vice versa). The researchers also found that the DNA methylation changes occurred within a critical window of the first week of life. As well, the methylation could be manipulated by giving certain chemicals to the offspring, suggesting that the effects of maternal care could potentially be reversed in later life.

STRESS RESPONSES SIMILAR

Professor Michael Meaney, one of the study's researchers, notes that while the work was done with animals, there are strong implications for human offspring as well. *"The brain regions that govern our stress responses are very similar in rat, monkey and human. Not surprisingly, the nature of the responses is also very similar."* However, as Meaney points out, while rats lick their children, humans do not, so it must be de-



"High-quality care in early childhood has a profound impact on the future well-being of the child"

termined what kinds of behaviours are comparable to the licking-grooming-nursing done by the animals.

REVERSE NEGATIVE EFFECTS WITH HIGH-QUALITY CARE

Professor Moshe Szyf of McGill University's Department of Pharmacology and Therapeutics and co-author of the study, notes that the study highlights just how critical those early years can be. *"The implications are that high-quality care in early childhood has a profound impact on the future well-being of the child. Negligent care early in life would translate into increased risk for behavioural and other pathologies. What is heartening in the study,"* Szyf adds, *"is that some of these negative effects may be reversible through improved care. It illustrates that this chain of transmission of vulnerability to behavioural and other pathologies from one generation to the next could be blocked by proper interventions early in the life of the child by providing high-quality child care,"* Szyf says. *"Providing such care opens up a better future for society as a whole,"* he adds. *"Policies which focus on early child care, could potentially have a profound impact on educational, behavioural and health outcomes later in adulthood, and thus have an important social as well as economic impact."* 🦋

LESS STRESS FOR MOM, BETTER HEALTH FOR BABY

by Liz Warwick

Prescriptions for a healthy pregnancy usually include good nutrition, moderate exercise and avoidance of alcohol, tobacco and other drugs. However, recent research suggests that high levels of stress should also be avoided as stress has been linked to emotional, cognitive and behavioural problems in offspring. Now, a study done by Canadian researchers has pinpointed some specific ways in which stress has an impact on brain development as well as potential ways to reverse the negative effects.

The researchers focused on the body's production of neural stem cells (NSCs) from which the central nervous system develops. They set up an experiment to see how stress might affect both the quantity and the functioning of the NSCs in mammals (in this case, hamsters). The researchers used common models for

reversibly inducing stress in animals and increasing maternal care: first restraining the pregnant females for short periods (called prenatal stress) and then, after the birth, moving the baby for brief periods into a special container lined with soft material (called postnatal handling) that subsequently results in more mother-infant interaction.

STRESS REDUCES NSCs

The researchers discovered that prenatal stress in mothers permanently decreased the number of NSCs in the offspring. Stress also decreased the proliferation of the NSCs in the brain. However, postnatal handling

reversed that negative effect in babies born to stressed mothers, putting their NSC levels close to those of babies whose mothers had never been stressed. The biggest gain, however, came from babies who received postnatal handling even though their mothers were not stressed. They had significantly more NSCs.

Tod Kippin, currently Assistant Professor in the Department of Psychology at the University of California at Santa Barbara and the study's lead researcher, notes that research in animals and humans has identified early environmental trauma as a common factor in many psychiatric conditions. *"This study identifies a developmentally important subset of neural precursors that are likely involved in the production of altered adult brain function and behaviour,"* he says, which could lead to better treatment as well as prevention. The study also underscores the importance of the perinatal period for optimal brain development. *"Generally these findings indicate that neurodevelopment of the offspring should benefit from reduced maternal stress prior to birth and increased maternal care following birth."*

HELPING PREGNANT WOMEN COPE WITH STRESS

Mark Ellenbogen, a Canada Research Chair in Developmental Psychopathology at Concordia University's Centre for Research in Human Development, notes, *"these findings underscore the importance of prevention programs, beginning in pregnancy, that help high-risk mothers structure their lives and cope with stress."* Ellenbogen adds that prenatal care might be expanded to include a greater focus on stress and stress-related problems. *"As well intervening in a baby's very early days may offer long-term health benefits,"* he says. *"These results indicate that responsive postnatal care is not only beneficial on its own, but can reverse the deleterious effects of a prenatal insult."* 🐾

"These findings underscore the importance of prevention programs, beginning in pregnancy, that help high-risk mothers structure their lives and cope with stress"



Ref.: Kippin TE, Cain SW, Masum Z, Ralph MR. Neural stem cells show bidirectional experience-dependent plasticity in the perinatal mammalian brain. *Journal of Neuroscience* 2004;24(11):2832-2836.

MORE PROOF THAT ADHD IS GENETIC

by Tracey Arial



Parents and teachers are frequently blamed as they struggle to cope with children who fail classes, perform badly on standardized tests or make few friends. Blame continues even after a child has been diagnosed with attention-deficit/hyperactivity disorder (ADHD), because the genetic nature of the disease is little recognized by the general public.

Researchers from 14 laboratories around the world found statistical proof that a genetic link exists between parents and children diagnosed with either inattentive or combined ADHD. Before working together, the researchers already knew that ADHD has a genetic component from previous research on families, twins and adopted children. They also knew

that dopamine-blocking medications work for 70% of people diagnosed with ADHD, and that several receptors might be involved. Their goal was to confirm an association between ADHD and the dopamine D5 receptor gene.

RARE INTERNATIONAL COOPERATION

The researchers began by recruiting participants from members of the ADHD collaborative network, which links researchers around the world. Centres represented in the study contributed data and at least three DNA samples from ADHD-diagnosed children and one or both parents to ensure consistency.

"This study is unique because it pulls together data from multiple settings, multiple families and multiple laboratories," says Dr. Russell Schachar, a senior scientist from the Department of Psychiatry at the Hospital for Sick Children in Toronto. "Politically, it's difficult to get scientists to contribute to that kind of study. I think that there have now been 16 or 17 risk factors identified in ADHD, and half of them have been identified with researcher Cathy Barr's laboratory, which is producing some of the world's best molecular research. At a scientific level, what she's been able to do, the kind of people she's been able to bring around her is impressive." "It's pretty clear that there's going to be a number of genes involved and we haven't even found them all yet," says Cathy Barr, from the Toronto Western Hospital Institute, and one of the Canadian researchers on the team.

In the end, it was the large study size that made results possible. Researchers compared the genetic makeup of 3,072 parents with that of 1,980 children in a statistical modelling process known as meta-analysis. They discovered a much higher incidence of a specific marker in both the diagnosed children and their parents than expected, thereby confirming the genetic region involved in ADHD.

"What a relief for these children's parents who are constantly being judged"

PARENTS NO LONGER BLAMED

"The most important change for parents with this study is that it further confirms the fact that ADHD runs in families. It gives parents support against teachers, doctors and others who imply that bad parenting somehow caused the disease," says Cathy Barr. "What a relief for these children's parents who are constantly being judged," says Francine Côté, General Manager of the Quebec PANDA group of associations, and mother of a young adult with ADHD. "These families live with rejection and criticism of their parenting skills. The impact of this research is major and we would encourage it to continue to improve the lives of children with ADHD who are our future adults." 🐾

Ref.: Lowe N, Kirley A, Hawi Z, Sham P, Wickham H, Kratochvil CJ, Smith SD, Lee SY, Levy F, Kent L, Middle F, Rohde LA, Roman T, Tahir E, Yazgan Y, Asherson P, Mill J, Thapar A, Payton A, Todd RD, Stephens T, Ebstein RP, Manor I, Barr CL, Wigg KG, Sinke RJ, Buitelaar JK, Smalley SL, Nelson SF, Biederman J, Faraone SV, Gill M. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. *American Journal of Human Genetics* 2004;74(2):348-356.

HOW WILL TOURETTE SYNDROME STRIKE WITHIN A FAMILY NEXT?

by Tracey Arial

Children who move or speak suddenly in inappropriate situations can embarrass themselves. When a child has Gilles de la Tourette Syndrome (GTS), such incidents can occur frequently. These vocal or motor tic episodes wax and wane in severity and diminish in frequency after the age of 19.



To try to find out how GTS runs in families, researchers at Yale University and at the University of Toronto studied 100 families over four generations that had been diagnosed with GTS. "Over 80% of the patients that we see at the clinic and participate in the studies have first-degree relatives—brother, sister, parent, child—that have the syndrome," says Paul Sandor, a Toronto-based clinician who participated in the study.

What was once seen as a rare disease is now recognized more prevalent making this type of research more important. "When I began to work with these patients about 23 years ago, it was believed that it was a disorder that occurred in one person in a million," said Sandor. "It is now estimated that the prevalence of GTS in the general population is somewhere between 1% and 3%. If you go to a special education class, the prevalence is between 7% and 15%."

To identify hereditary patterns from generation to generation, researchers screened two large multi-generational families for 13 different markers and 25 variations in gene sequences on chromosome 17. They then expanded the study group to

"It's the first pretty solid indication that one of the genes would predispose an individual in a specific way"

include four large families, and later an additional 96 nuclear families, each with one or two diagnosed children.

"Tourette syndrome is in need of better treatment," said Cathy Barr, a Canadian researcher from the Toronto Western Hospital Institute involved in the study. The problem is complex, however. "It now seems probable that half a dozen or more genes are involved," says Sandor. "Being able to identify them early would help put in place interventions that would minimize the impact if, and when, the symptoms were to appear."

Results indicate that three genes in one region of chromosome 17 might protect

individuals from, or make individuals susceptible to GTS. The first two genes determine brain development and function. The third gene produces a protein that directs the manufacture of microtubules, which are crucial for pulling chromosomes apart during cell division and connecting nerve cells.

These results have since been duplicated on a third group of 200 families in Montreal, says Dr. Guy A. Rouleau, a geneticist at the Université de Montréal Institute on Brain research and the leader of a group linked to the Tourette Syndrome Association International Consortium for Genetics. "It's the first pretty solid indication that one of the genes would predispose an individual in a specific way," he said. "We're going to be doing many more markers in this area... We're also continuing to collect families."

"Telling parents how GTS runs in families would really help," says Sylvain Chouinard, the Director of the Tourette clinic at Sainte-Justine Hospital in Montreal, which treats more than 200 families in which one or more people have been diagnosed with GTS. The most common question he hears from his patients is: "how will my disease show up in my children?" 🦋

Ref.: Paschou P, Feng Y, Pakstis AJ, Speed WC, Demille MM, Kidd JR, Jaghori B, Kurlan R, Pauls DL, Sandor P, Barr CL, Kidd KK. Indications of linkage and association of Gilles De La Tourette Syndrome in two independent family samples: 17q25 is a putative susceptibility region. *American Journal of Human Genetics* 2004;75(4):545-560.

UNLOCKING MYSTERIES OF MULTIPLE SCLEROSIS

by Liz Warwick

For the estimated 50,000 Canadians living with multiple sclerosis (MS), understanding the disease's root causes is a key step toward making informed decisions about treatment and care. However, this information becomes even more relevant when a woman who is considering having a baby needs to evaluate the risk of her child developing MS.

Researchers believe that MS happens when genes and environmental factors lead the body to attack the myelin sheaths or coverings of the nerves and their fibres (axons) in the central nervous system (brain and spinal cord). The inflammation and loss of the myelin and axonal damage impede the normal flow of nerve impulses along the nerve fibres, resulting in a wide-range of symptoms: visual disturbances, fatigue, coordination and balance problems, weakness in limbs and muscle stiffness among others.

MS RISK GREATER IN MATERNAL HALF-SIBLINGS

A recent study led by Canadian researchers suggests that mothers have a significant effect on risks their children will develop MS. The researchers collected and analyzed data about the occurrence of MS in full-siblings and half-siblings to see if there were so-called "parent of origin effects." They found that for maternal half-siblings, the risk of developing the disease was 2.35%, while the risk for paternal half-siblings was 1.31%. The research also showed that full-siblings risk of developing the disease was 3.11%.

Doctors A.D. Sadovnick of the Department of Medical Genetics and Faculty of Medicine, at the University of British

Columbia, and George Ebers of the Department of Clinical Neurology, Oxford University, U.K., were the lead researchers for the study. "While the results show a maternal effect on the risk of developing MS, this certainly does not imply a clear-cut causal relationship," Sadovnick cautions. "This is just one of many factors," she says. The study's findings, coupled with other research Drs. Ebers and Sadovnick have done as part of the Canadian Collaborative Project on Genetic Susceptibility to MS, indicate that interventions to prevent MS or reduce the risk of developing it may need to happen in the prenatal or early pregnancy period. "This study gives clear indications that we will have to consider early intervention," adds Dr. Sadovnick.

GIVING PARENTS INFORMATION THEY NEED

Dr. William J. McIlroy, National Medical Advisor for the Multiple Sclerosis Society of Canada, points out that the half-sibling study is part of the genetics susceptibility study and this research will help those interested in bearing children. "The half sibling results mean that people with MS and



"This study gives clear indications that we will have to consider early intervention"

their relatives can now be given concrete practical information about the risk of developing MS themselves, and the risk to unborn offspring," he says. These studies hold out hope for people with MS and their families, not just of better treatments and more knowledge, but also for prevention. ♻️

Ref.: Ebers GC, Sadovnick AD, Dymnt DA, Yee IML, Willer CJ, Risch N. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. *Lancet* 2004;363(9423):1773-1774.

"NIPPED" GENE HOLDS KEY TO BIRTH DEFECT

by Liz Warwick

Cornelia de Lange syndrome (CdLS) is a genetic disease that affects an estimated one in 10,000 children. Named after the Dutch pediatrician who first described the symptoms, it has long confounded both researchers and families. CdLS produces a variety of symptoms, including cognitive retardation, impaired growth, limb defects, feeding problems as well as specific facial abnormalities. The effects range from mild to severe, making diagnosis difficult.

However, pioneering work by researchers from Canada and the United States has pinpointed the gene that causes many cases of CdLS. The new finding not only offers a chance for an earlier diagnosis of the disease, but also paves the way for a better understanding of other genetically-based birth defects.

The researchers analyzed the genome (the entire genetic makeup of an individual's DNA) of families in which more than one member had CdLS. They eventually narrowed down four key regions, finally identifying mutations in a large gene they called NIPBL, which stands for Nipped B-like. In fruit flies, mutations in a similar gene, Nipped-B, can produce an abnormal wing that looks like it has been "nipped" or had a bite taken out of it. The Nipped-B gene, in both insects and humans, regulates biological signals that affect the development of many different systems in the body.

GENE HOLDS KEY TO UNLOCKING OTHER DISEASES

Identification of the NIPBL gene opens the way for a more accurate diagnosis of CdLS, says Dr. Ian Krantz of the Division of Human Genetics at The Children's Hospital of Philadelphia, one of the study's lead researchers. "Finding a change in the CdLS gene—what we term a 'mutation'—allows us to test parents for carrier status as well as providing a prenatal test for concerned families,"

Dr. Krantz says. However, the vast majority of children have a new, not inherited, NIPBL mutation. Dr. Krantz, who operates the only clinic in the world to offer comprehensive services to children with CdLS, adds that the gene's discovery has led to increased interest in studying NIPBL and its effects. "Since NIPBL is a master switch that regulates many downstream genes, one of our goals is to identify what those downstream targets are," he says. "This will allow us to isolate genes that are responsible for the individual components seen in CdLS, such as isolated

congenital heart defects, cleft palate, hearing loss, etc. All of this will lead to better diagnosis and management for children and families affected by CdLS."

BETTER DIAGNOSIS POSSIBLE

"The NIPBL gene discovery is critically important for families who may not be aware that their child suffers from the disease," says Kalia Kellogg, Director of Communications for the Cornelia de Lange-USA Foundation. Families sometimes spend years searching for a proper diagnosis of CdLS, especially if the child has mild symptoms. "Genetic testing will resolve this problem," Kellogg adds, "and help parents gain access to interventions and therapies that may make a difference in a child's long-term cognitive, behavioural and physical development." Testing also offers a certain measure of comfort to families: "This has helped families realize that the disease stems from a random genetic mutation. It is not something they did or didn't do to their child," concludes Kalia Kellogg. 🦋

"This has helped families realize that the disease stems from a random genetic mutation. It is not something they did or didn't do to their child"



Ref.: Krantz ID, Mccallum J, Descipio C, Kaur M, Gillis LA, Yaeger D, Jukofsky L, Wasserman N, Bottani A, Morris CA, Nowaczyk MJM, Toriello H, Bamshad MJ, Carey JC, Rappaport E, Kawachi S, Lander AD, Calof AL, Li HH, Devoto M, Jackson LG. Cornelia de Lange syndrome is caused by mutations in NIPBL, the human homolog of *Drosophila* *Melanogaster* Nipped-B. *Nature Genetics* 2004;36(6):631-635.

MMR VACCINE AND AUTISM: PARENTS CAN PUT THEIR FEARS TO REST!

by Eve Krakow

Over the last seven years, concern that the measles-mumps-rubella (MMR) vaccine might cause autism has led to much agony for parents as they weighed the pros and cons of getting their child vaccinated. But a recent study that looked at over 5,000 children and found no link between MMR and autism should finally put parents' fears to rest.



"People have to remember what it means not to vaccinate a child. About one million children worldwide die each year from measles"

The controversy began in 1998, when Dr. Andrew Wakefield reported a possible association between the vaccine and autism. Although subsequent studies failed to substantiate this claim, the damage was done. Parents were worried; vaccination coverage levels dropped.

This latest study looked at the medical records of over 5,000 children born in 1973 or later to determine whether MMR vaccination is associated with an increased risk of autism or other pervasive developmental disorders (PDDs). It used the U.K. General Practice Research Database, which contains data on several million individuals in the U.K. To conduct their study, the researchers generated a sample of about 1,400 children with autism or other PDDs.

"We found no evidence whatsoever for any association between MMR and autism," says Éric Fombonne, Canada Research Chair in Child Psychiatry, and one of the study's researchers. He notes that this kind of case-control study is very precise. *"It would be highly unlikely that there would have been any effect of MMR that we would not have captured."*

He believes this new evidence will help change people's attitude towards the vaccine. *"Our study adds a new, major piece of evidence. Now it's up to first-line health professionals to be convincing about this study*

and to say, there is absolutely no evidence of this association."

"People have to remember what it means not to vaccinate a child," he adds. *"About one million children worldwide die each year from measles."* And while most of these deaths occur in developing countries they occur in developed countries too. He cites the case of Ireland where, in 1999, following the MMR scare, vaccination coverage was down to 74%. This led to a massive epidemic, in which 150 children became severely ill and three children died.

Dr. Emmett Francœur, a pediatrician at the Montreal Children's Hospital, says that while the scare did not cause vaccination coverage levels to drop significantly in Canada, it has led to lengthy discussions with parents whenever it was time for a child to get the MMR vaccination. He says this new study is extremely reassuring.

"Because this was a case-control study and was so carefully done, and included samples prior to the time that this issue was even discussed in the population, it carries a lot more weight than all the other studies," he explains. *"So we feel a lot more confident now saying there really is no association."*

"This new evidence sends a clear and firm message," he says. *"When talking eyeball to eyeball with a parent who's worried about his or her child, if there's any molecule of doubt left in your body, he will notice it. Now, with this study, the molecules of doubt have been dissipated."* ❧

AUTISM

AND VOICE PROCESSING

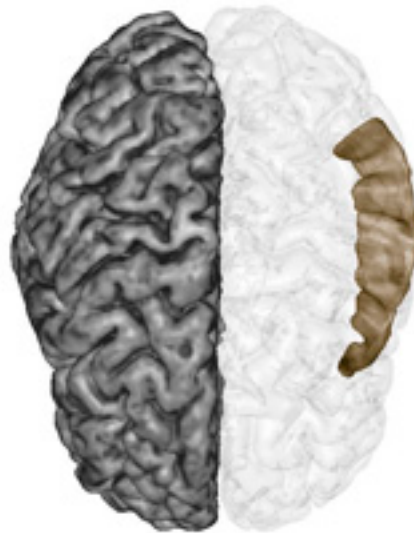
by Eve Krakow

Autistic children often have trouble making sense of social situations: they do not instinctively read the emotional or affective state of others. While previous research has focused on their difficulty in decoding faces, a new study on their perception of voice suggests that the way their brain processes auditory information might also be a factor.

The study involved five male adults with autism and eight healthy male adults. Researchers used functional magnetic resonance imaging (fMRI) to determine which areas of the brain were activated when the subjects listened to various sounds, some vocal and some non-vocal. In four of the five autistic individuals, no significant activation of the voice-specific area of the brain was observed. As well, when subjects were later asked to recall the sounds they had heard, the autistic men recalled a very low proportion of vocal sounds compared to the control subjects.

"It has been known for some time that autistic children have problems extracting information in faces and in voices, but so far the research on the neurobiological basis has focused on the perception of faces," says Pascal Belin, a professor at the Université de Montréal and one of the study's researchers. *"This experiment suggests that autistic individuals might have a similar type of deficit for the perception of voices."*

It is important to note that the experiment did not focus on speech, but on vocal sounds. *"Voice contains much more information than speech,"* Belin explains. *"It allows*



■ Cerebral activation
in response to vocal sounds

"This research confirms that people with autism really are hardwired to process the world differently"

us to infer a lot about a person's identity and affective state. The ability to extract such information is very important for the development of young children," he notes. *"During the first few months of life, most of the information newborns extract from their parents is not linguistic, but affective and identity-related."*

Dr. Wendy Roberts, a developmental pediatrician at the Hospital for Sick Children in Toronto, says this research confirms that people with autism really are hardwired to process the world differently. *"This means we have to really work at understanding, par-*

ticularly in the early years when the brain is more pliable, how to push intervention so that we can influence the development of the pathways that may otherwise remain non-functional."

Dr. Roberts says that in babies with autism, their attention to voice changes by the time they are 18 months old. *"They'll hear a tiny little fan noise that we wouldn't hear, and yet you can say anything to them, call their name, and they're not paying attention. So we really believe it's around the one-year mark, between 9 and 15 months, that something changes in the evolution of a brain that has that vulnerability for autism, and voice processing becomes different."*

Not only can this kind of research be used to try and track exactly when these changes occur, but it may eventually provide a way of identifying the children at highest risk, so as to better allocate the limited resources available. *"Early interventionists and speech pathologists are doing what they can, but if we could narrow down the group at highest risk, if we could really get in there intensively with that child at 9-10 months, maybe we could influence how that brain develops,"* concludes Dr. Roberts. 🐾

THE VACCINATION GAME

by Eve Krakow

When deciding whether or not to vaccinate their child, parents weigh the benefits against the risks. Yet their choice is also influenced by other people's choices. For example, if everyone around them is vaccinated, they may be tempted not to vaccinate thinking that their child is protected through herd immunity.

"In this case, even a slight perceived risk can tip the scales in favour of non-vaccinating behaviour and cause a decline in vaccine uptake," says Chris Bauch, a mathematician at the University of Guelph, Ontario.

Bauch and David J.D. Earn, a mathematician at McMaster University, Ontario, used "game theory" to analyze human behaviour when it comes to making decisions on vaccinating their child. They believe such modelling could be of use to policy-planners.

Game theory involves understanding strategic interactions in a group. *"The best example is a game like poker, where you pick your strategies according to what you think other people will do,"* explains Bauch. *"You try to maximize your payoff."*

The key prediction made in this research is that vaccination coverage levels will tend to recover more slowly after a scare than

the rate at which they initially dropped. More generally, the authors want to emphasize that when vaccination is voluntary, high coverage levels are inherently instable. *"Voluntary policies are victims of their own success,"* says Bauch. *"Once coverage is sufficiently high, people get complacent."*

Edward Kaplan, a professor of public health at the Yale School of Management, specializes in the use of mathematical modelling to help make better decisions. He suggests one way to counter the problem raised by this study would be to provide incentives for people to vaccinate, such as reductions in insurance premiums. *"When individuals act in their own interests, one rarely arrives at a result that is best for the group."*

Bauch believes this kind of research could influence policy-makers. However, it will take more time before a model can be developed to answer specific policy questions. ♻️

"Voluntary policies are victims of their own success"

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