MEDNIK: A New Genetic Syndrome

A one of a kind disease, MEDNIK was recently identified in Quebec. It is a genetic disorder that developed in the province’s Kamouraska region. “While it is an interesting discovery, it also reveals the potential of genetic exploration” notes Patrick Cossette, a CRCHUM researcher and Director of the Canadian team responsible for the study.

By Liliane Besner

FOUNDER EFFECT

This syndrome encompasses a series of serious afflictions: severe mental retardation, deafness, cerebral motor disorders, serious intestinal problems and scaly and thick skin. The severity of these symptoms often results in death within the first two years of life. However, some people, like 15-year-old Éthienne Michaud, survive much longer. Michaud is the oldest of the eight cases identified to date.

The genetic mutation responsible for MEDNIK was discovered in five families from the lower Saint Lawrence region with common ancestors who emigrated from France between 1608 and 1759. Since it is a recessive disorder, the mutated gene was probably handed down from one generation to the next because of the founding population’s closed genetic pool. As such, MEDNIK can be viewed as a disease arising from a founder effect. However, it is a rare disease and so far appears to be limited to descendants of the Kamouraska population.

MAKING AN INFORMED DECISION

Because of the recessive mode of inheritance, both parents have to be mutation carriers and both abnormal copies of the gene have to be present at conception. As such, when both parents are carriers, there is a one in four chance that they will have a child afflicted with MEDNIK syndrome. However, as Dr Cossette explains, “families identified as being at risk can now be screened to determine whether they are carriers or not. If so, amniocentesis can determine whether the future baby will have the syndrome”.

Éthienne’s mother, Julie Leclerc-Michaud, wishes that she could have benefited from genetic testing. Her oldest son displayed many serious symptoms and at birth was viewed as an “accident of nature.” Fortunately, her two subsequent children are in good health but she was only certain they were syndrome-free after giving birth to them. She is happy that her younger son, her daughter and her niece and nephews who, thanks to genetic screening, will now be able to have families of their own without fear: “They won’t have to rely on luck to avoid bringing a severely affected child into the world.”

UNDERSTANDING OTHER DISEASES

In addition to limiting the number of people affected with MEDNIK syndrome, this discovery could become an important key to understanding mental retardation and deafness. The guilty gene is the AP1S1 gene, whose normal role is to initiate the transportation of several proteins necessary for cell organization and development. It also plays a key role in the creation and survival of embryos. When it is altered, this gene results in a disorganized molecular functioning, leading to modifications in the normal development of various neuronal networks that affect the spinal cord, the inner ear and the brain or skin of individuals with MEDNIK syndrome.

By inactivating this gene in zebrafish, Dr Cossette’s team noticed that it provoked abnormal spinal cord development and various other malformations. Moreover, when the fish were injected with the normal human AP1S1 gene, the developmental abnormalities did not occur, which was not the case with the mutated version of the same gene.

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"The knee is a complex joint; but it is also so unstable that you would think it was invented on a Friday afternoon," says Jacques de Guise, a CRCHUM researcher and Director of the Imaging and Orthopaedics Research Laboratory, professor at the École de technologie supérieure, and the Canada Research Chair in 3D Imaging and Biomedical Engineering. It is not surprising, therefore, that it is easily injured. In fact, 70% of athletes (skiers, long-distance runners, hockey players, etc.) with knee injuries never completely recover because their original biomechanical "signature" is not re-established.

Jacques de Guise

Friday’s child – KneeKG

"KneeKG", which stands for kinematic knee graphic (or CKG for cinematic knee graphic), is a bit like an electrocardiogram of the knee, as the acronym implies. It consists of a harness studded with electromagnetic motion captors. Once attached to the tibia and the femur, it makes it possible to sketch a precise portrait of the knee’s articular mechanics along all of its axes while the patient is walking on a treadmill or making bending movements. This invention is something of a godsend for the growing ranks of Baby Boomers, whose knees often cannot keep up with their desire to maintain an active lifestyle. It is also of vital importance for their grandchildren, whose increasing involvement in sporting activities brings with it a greater risk for knee injuries.

Since KneeKG offers improved treatment possibilities, it will also lead to reduced social costs by lowering, if not eliminating, the worsening of a given disease or injury, which in turn will reduce interminable treatments and costly surgery, long periods of convalescence or permanent invalidity. In many cases, it will also lead to a more rapid return to work and to normal activities.

Jacques de Guise

MAKING THE RIGHT DIAGNOSIS

The challenge for health professionals is to reduce the time needed to make the right diagnosis of the problem and therefore optimise recovery. To meet this challenge, de Guise and his team developed KneeKG, a revolutionary technique for knee evaluation and rated as one of the 15 most promising inventions of 2008 by the Fonds de la recherche en santé du Québec. What sets this technique apart is that it allows for real-time 3D analysis of the knee during movement and while supporting the body’s weight, something which cannot be done by the traditional tools of analysis, X-rays or magnetic resonance.

KneeKG does not replace the latter two techniques; rather, it provides valuable new information about how the knee works, which helps clinicians to prevent, detect and treat pathologies such as arthrosis, tendinitis or torn ligaments and other knee injuries. “KneeKG helps clinicians make the right diagnosis,” says de Guise, “which makes it possible to design a more effective treatment or rehabilitation plan." Making the right diagnosis also helps direct patients to the right treatment, the appropriate health professional, at the right time. The device could even delay or eliminate the need for early surgical intervention.

BOON FOR BABY BOOMERS AND THEIR GRANDCHILDREN

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WORLDWIDE DISTRIBUTION

KneeKG’s more than $1 million in development costs over a ten-year period were funded by the Canada Foundation for Innovation, the National Sciences and Engineering research Council of Canada, the Fonds québécois de la recherche sur la nature et les technologies, Valorisation Recherche Québec, and the Canada Research Chairs Program.

The Clinique Emovi in Laval, Quebec, holds the exclusive commercialization licence for KneeKG and will begin worldwide distribution (Canada, USA and Europe) in June 2009.

By Monique Guilbault

Jakub Domiński
The enigma of cystic fibrosis related diabetes

Cystic fibrosis (CF) is a deadly genetic disorder for which there is no known cure. However, thanks to the development of comprehensive treatment programs, the life expectancy of people with CF has increased from four years old in the 1960s to around 40 years old in 2009. The bad news is that this relative longevity can come at a heavy cost: 20% to 40% of people with CF develop cystic fibrosis related diabetes (CFRD), the cause of a sixfold increase in morbidity and mortality in this population.

By Monique Guibault and Richard Ashby

A UNIQUE FORM OF DIABETES

CFRD is a unique form of diabetes specific to CF that displays certain aspects common to both types of diabetes that occur in the non-CF population (i.e., insufficient insulin production and insulin resistance). Diabetes and the hyperglycaemia (high blood sugar levels) that precedes it accelerate lung deterioration up to two years before it is diagnosed. And therein lies a considerable problem: if it is not detected at an early stage, there is a missed treatment opportunity which could delay the onset of CFRD and hinder better management of its consequences.

Help is on the way, however. With a $900,000 grant from the Canadian Cystic Fibrosis Foundation, Dr Yves Berthiaume, a CRCHUM researcher and member of CHUM’s pneumology department and CF clinic, has assembled a multidisciplinary team of experts to conduct a three-year study on the causes, consequences and current detection methods of CFRD.

IDENTIFYING THE CAUSES

This research program is the first of its kind in Canada to adopt a multidisciplinary approach to CFRD. Dr Berthiaume’s team includes endocrinologists, nutritionists, immunologists, physiologists, physicians who treat CF patients and experts in health care management. “Our goal”, says Dr Berthiaume, “is both to investigate the causes and consequences of CFRD and to assess current detection methods. A team of this nature will enable us to develop an innovative and comprehensive research program.”

Until recently, conventional wisdom had it that CFRD was the result of damage caused by cystic fibrosis itself. Many believed that insufficient insulin production that controls blood sugar results was the result of pancreatic scar-
Prostate cancer: moving towards a molecular signature?

Should prostate cancer be treated when it first appears? If so, then how does one objectively assess the risk of cancer progression and then propose an appropriate treatment strategy? Specialists are faced with these tricky questions on a daily basis. Finding the answers is the aim of Dr Fred Saad, researcher with the CRCHUM and the University of Montreal Research Chair in Prostate Cancer. He also heads up a pilot project sponsored by the Terry Fox Institute to assess biomarkers that promises to shed light on these significant issues for patients and clinicians alike.

**By Liliane Besner**

**TO TREAT OR NOT TO TREAT**

Prostate cancer is the most widespread cancer and the third leading cause of death among men. In 2008 alone, 24,700 new cases were diagnosed in Canada. Early detection programs combining digital rectal examinations and measurement of prostate specific antigen (PSA) levels in the blood have tripled the detection of “non-significant” cancers; that is, cancers with a very low risk of becoming metastatic. Some of these cancers develop very slowly and can be present for many years without ill effect on health or life expectancy, in which case clinicians must be careful not to react with unnecessarily aggressive treatments. At the same time, it is important not to overlook other cancers that are more likely to progress to a life threatening stage, which must be treated quickly and decisively. How do we diagnose and differentiate between these two scenarios?

**IDENTIFYING BIOMARKERS**

At present, prostate cancers are detected using a three-pronged approach: the PSA blood test, a digital rectal examination and then a biopsy. The objective of Saad’s pilot project is to identify a set of unique biomarkers that can further inform clinicians about the probable progression of each patient’s case and allow for a better-tailored course of treatment. As Saad explains, “the hypothesis is that every detected cancer has a specific molecular signature that will immediately reveal the probability of its progression and whether or not it should be treated. We must modulate treatment as a function of the cancer’s developmental profile, the patient’s life expectancy and the anticipated effectiveness of treatment.” Therein lies the importance of the search for biomarkers and other diagnostic tools.

**TERRY FOX INITIATIVE**

Fred Saad co-directs the cancer research theme at the CRCHUM and is a leader in the clinical investigation of new therapeutic strategies for aggressive cancers (genetic medicine, vaccines, innovative chemotherapy, targeted monoclonal antibodies, etc.). He is also the director of a vast pan-Canadian project bringing together seven centres of excellence in prostate cancer research, with the objective of gathering clinical data to validate the predictive value of specific biomarkers. “Because prostate cancer is extremely complex,” notes Saad, “it is crucial that researchers work in concert to test the most promising parameters; we will progress more quickly if we work together rather than in isolation.” He expects the project to yield clinically useful biomarkers within the next three to five years.

As Chair of the National Cancer Institute of Canada’s Genitourinary Group, Dr Saad is in a privileged position to oversee the transition from laboratory findings to clinical applications. His hope is that this pilot project will make it possible to map a whole series of molecular markers for prostate cancer that will enhance the prediction and decision-making processes. It will also constitute a major step forward for practitioners, patients and their families in the evaluation of various treatment options.

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According to Dr Cossette, these findings pave the way for a better understanding of the role of the various API gene complexes and could eventually be identified as playing a role in mental retardation, deafness or neurocutaneous disorders. Filled with both enthusiasm and humility, Dr Cossette notes that “it is truly fascinating to realize just how many enigmas are buried in phenotypes.”

Dr Cossette’s research is funded by: the Canadian Genetic Diseases Network, the Canadian Institutes for Health Research, the Fonds de la recherche en santé du Québec, Genome Canada and Genome Quebec.

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**EXCELLENCE ■ INNOVATION ■ TRANSFER**

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