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IDENTIFICATION OF GENES CAUSING DEFECTS IN VITAMIN B_{12} METABOLISM

Montreal, December 10, 2002 – Investigators at the University of Calgary and McGill University have identified genes that underlie two severe diseases of vitamin B_{12} metabolism. The two diseases, known as the *cblA* and *cblB* forms of methylmalonic aciduria, may produce brain damage, mental retardation and even death if not detected in infancy or early childhood.

Melissa Dobson, a graduate student at the University of Calgary working with Roy Gravel PhD in the Department of Biochemistry and Molecular Biology, is lead author of two papers reporting the identification of the two genes. The genes were first identified in bacteria and then traced to their human counterparts. She credits the human genome project with her breakthrough. “We can now compare human and bacterial DNA sequences to find human genes,” states Dobson. “This was made possible by the availability of the sequence of the complete human genome.”

To prove whether she and colleague Daniel Leclerc, PhD, had identified the correct genes, she approached her McGill collaborators, Dr. David Rosenblatt and Dr. Thomas Hudson, for help in screening patients. The McGill University Health Centre (MUHC) has a world-renowned diagnostic facility and cell bank for patients with genetic diseases involving vitamin B_{12}. Using Genome Quebec’s MUHC -based sequencing centre, Dobson and her colleagues confirmed the presence of mutations in DNA from patients with the two diseases.

“We have identified two different genes that are critical to the processing of vitamin B_{12} by finding mutations in patients who have particular forms of methylmalonic aciduria,” according to Dobson. Methylmalonic acid is a chemical intermediate in the breakdown of proteins and other substances. It accumulates in the body and is excreted in large amounts in the urine because the blocks in the processing of vitamin B_{12} prevent its metabolism.

Identifying the genes that cause cblA and cblB represents a landmark breakthrough for patients suffering from both forms of the disease. “The discovery will make possible DNA testing for carriers and early prenatal diagnosis. This is important because treatment can be started during pregnancy,”

says Rosenblatt. Fortunately, many patients can be treated with high dose vitamin B_{12} supplements and a diet that is low in protein.

“This research will lead to better understanding of the disorder and provides hope to those families living with this disease,” adds Kathy Stagni, Executive Director of the Organic Acidemia Association, a nonprofit organization that supports families with inherited metabolic disorders.

This research is published in the November 26 issue of the Proceedings of the National Academy of Sciences (USA) and the December 15 issue of Human Molecular Genetics.

This study was supported by the Canadian Institutes of Health Research (CIHR), the National Institutes of Health (USA), and the March of Dimes Birth Defects Foundation.

The scientists are members of the Medical Genetics Group of the CIHR and the Canadian Genetic Diseases Network. Based at McGill, the Medical Genetics Group has existed since 1972, a record for sustained federal funding for such research.

- 30 -

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