# Diabetes-associated fat disorder traced to genetic mutation

Canadian researchers have discovered that Dunnigan-type familial partial lipodystrophy (FPLD), a body-fat disorder that often leads to diabetes, is caused by a mutation of the lamin gene (*LMNA*) on human chromosome 1q21-22.

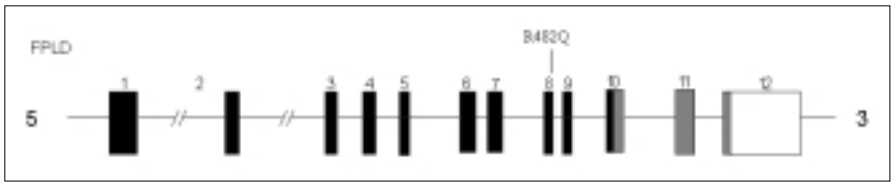
The finding, by Drs. Robert Hegele and Henian Cao of the John P. Robarts Research Institute in London, Ont., is the first definitive indication that degenerative disorders of fat cells can be caused by mutations. Hegele says it may point the way to a better understanding of diabetes, as well as of fat distribution in healthy individuals, and of the lipodystrophy that occurs in patients receiving protease inhibitors for AIDS.

"Central fat leads to diabetes. These people [FPLD patients] have an extreme form of central fat. If we can understand better the mechanism of disease in these people, it could be applicable to the more garden-variety form of obesity," he says.

In the Jan. 1 issue of *Human Molecular Genetics* (available early online at **www3.oup.co.uk/hmg/**), Hegele and Cao report using Robarts' DNA sequencing technology to find the mutation responsible for FPLD (*LMNA* R482Q) in the lamin gene that codes for 2 proteins, lamin A and lamin C.

Patients with FPLD (**www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?151660**) have normal fat distribution at birth. Following puberty, fat accumulates around their neck, shoulders, the "buffalo hump" area between the shoulders, and the genitalia. At the same time, fatty tissue atrophies in the limbs and buttocks, giving those affected a lean and muscular appearance. The disorder is also often associated with profound insulin resistance and diabetes, high blood pressure and cholesterol, and heart disease.

Hegele, an endocrinologist at the London Health Sciences Centre and director of Robarts' Blackburn Cardiovascular Laboratory, and Cao, a research fellow, used a rapid genotyping test to locate the *LMNA* R482Q mutation in 22 FPLD-affected patients. The mutation was not found in 23 family members unaffected by FPLD, or in 1000 control subjects representing people of Caucasian (276), South Asian (243), African (169), Chinese (160), Oji-Cree (76), and Inuit (76) descent.




**Schematic diagram of the human lamin A/C (*LMNA*) gene, showing the position of the FPLD mutation. The mutation is in the eighth exon, and alters the DNA sequence that would normally encode the amino acid arginine (R) at position 482. The mutation encodes glutamine (Q) instead. Hence, the mutation is designated R482Q.**

The search for an FPLD-causing mutation had been previously pinpointed by other researchers to a 120-gene section of chromosome 1. Aware that another disease causing heart difficulties and loss of muscle cells had been traced to mutations in the *LMNA* gene, Hegele and Cao decided to focus their research there.

In the Human Molecular Genetics paper, the Robarts researchers report that they have applied for a patent on "novel concepts and materials derived from this work." — *David Helwig*, London, Ont.

## Briefly . . .

### Gene therapy hits a snag

Using gene therapy to combat cancer depends on delivering the genes to the tumour on a "vector" — usually an adenovirus thought to be harmless to the host. But long-term follow-up of survivors of gene therapy for brain glioblastoma shows that the therapy causes chronic brain inflammation (*Nat Med* 1999;5:1256-63). Three months after glioma growth was inhibited through gene therapy, researchers found activated macrophages/microglia and astrocytes, positive T cells, secondary demyelination, widespread immunoreactivity to a herpes simplex virus 1 enzyme, and the genome of the adenovirus vector throughout large areas of the brain. This could pose an important stumbling block for the future use of gene therapy.

### Persistence of memory

Our understanding of the immune response to infection, and of immunization, may be revolutionized by recent research into T cells. The immune response after vaccination results from the property of "memory," which is established in appropriate lymphocytes. It was thought that these "memory T cells" are activated when they "see" the offending antigen, together with a major histocompatibility protein, and that there was a continuing requirement for antigen stimulation for memory T cells to work. Now 2 studies in mice show that memory T cells — both CD4 and CD8 cells — never forget (*Science* 1999;286:1377-81,1381-3). Even in mice genetically altered to lack major histocompatibility complex proteins and never exposed to the antigen before, memory T cells launched an immune response to invading pathogens.