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Uncovering the genetic causes of childhood diseases

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MOST CANADIANS are generally aware that genetic research has become a vital aspect of progress in the health sciences.

But fewer realize that when children are involved, that vital significance of genetic factors needs to be doubled, with childhood conditions including Type I diabetes, asthma, autism, childhood cancers and cystic fibrosis all strongly congenital in origin.

"In 96 per cent of the chronic disorders in kids there is a genetic basis or a genetic tendency," explains Dr. Stephen Scherer, a senior scientist and director of The Centre for Applied Genomics at The Hospital for Sick Children in Toronto.

"Genetic factors are behind conditions triggering 71 per cent of the admissions to pediatric hospitals."

What is so important and exciting to scientists like Dr. Scherer is that the rate of progress in genetic investigation worldwide has been dizzying. Not only have some 1,900 of the estimated 6,000 disease genes been identified, he notes, but the vast majority of those have been in the

last five years.

Sick Kids began consistent and serious investment in genetics research from the early seventies, a period when rewards for the effort were still well over a decade away. It was a far-sighted focus that went on to yield the identification of the genes linked to cystic fibrosis and muscular dystrophy at the leading Canadian pediatric hospital.

"We have contributed now to the discovery of well over 30 different disease genes, which I think is unprecedented across the world," says Dr. Scherer, who like most of his colleagues at Sick Kids also has an appointment at the University of Toronto. "We were the first in Canada to create a human genome centre and now The Centre for Applied Genomics actually supports over 500 individual scientists from across Canada and around the world."

The combination of top scientists, state-of-the-art technology and close collaboration with a strong statistical analysis and clinical genetics group is a key factor behind the hospital's

remarkable success in the field, a discipline which Dr. Scherer believes is within a decade or less of identifying all 6,000 disease genes.

"People want to come here from all over the world to access the technology and information we have," Dr. Scherer remarks. "We are very dependent on computational biology and now 50 per cent of this work is done on a computer."

Dr. Scherer isn't only the administrative head of The Centre for Applied Genomics; he's also an active Sick Kids senior scientist, currently working as a project leader on a multi-million dollar, four-year autism genome project, which is an international effort involving 170 scientists from 10 countries to uncover autism susceptibility genes for eventual translation into clinical interventions. The project is currently funded by the U.S.-based National Alliance for Autism Research and the National Institutes of Health.

If the cost of the study sounds substantial, consider that the estimated 105,000 people in Canada with what today is called autism spectrum dis-

order. Autism-related services, which are largely not based on sound scientific investigation, cost some \$3-billion annually. Cost-benefit aside, autism is one of the most severely handicapping of childhood conditions.

And some 3,000 new cases come to light in Canada each year. Most disturbingly, that's a rate of diagnosis that has quadrupled in the last decade for reasons that remain largely perplexing. Uncovering the relevant genes will be a milestone in unraveling that perplexity.

"When you have made a genetic discovery, you have a target to direct your best therapeutic and diagnostic candidates," says Dr. Scherer, reflecting on the 1989 Sick Kids identification of the cystic fibrosis gene which led to new diagnostics for that disease. "With autism, we know there's a genetic component by studying twins. The whole scientific basis of studying of autism is very new. And I think most people in the field feel that genetics is the way to go."

Genetics is very likely to prove the way to go with most childhood dis-

eases, although the complexity involved is going to vary considerably. While cystic fibrosis is a single-gene disorder, for example, diseases such as diabetes and cancer are thought to likely have multiple causal genes.

The complexity does not discourage Dr. Jayne Danska, a Sick Kids senior scientist heading a \$10.9-million investigation into the functional genomics of Type I diabetes (formerly called childhood-onset or insulin-dependent diabetes). The project has funding from Genome Canada/Ontario Genomics Institute, Juvenile Diabetes Research Foundation, the Canadian Institutes of Health Research and Sick Kids Foundation.

"We are using genome-wide technologies to study Type I diabetes, a relatively common disease with a complex genetic origin," says Dr. Danska. "Many different genes are interacting."

"Complex genetic diseases present a big challenge to finding genes using conventional methods that have been so successful for single-

gene diseases like cystic fibrosis and Tay-Sachs," she adds. "We want to understand these complex genetics; to identify genetic variants associated with risk for diabetes and to understand what those variants do at a functional, cellular level."

A common misperception is that Type I diabetes is "cured" or at least completely controlled by the use of insulin. In fact, while intense management of the condition can often delay complications the disease is nonetheless a leading cause of blindness, kidney failure and non-traumatic amputation in Canada.

That's a disease that needs to be battled, and genetic research can change the dynamics for this and many other childhood illnesses.

"Canada is really known worldwide for progress and seminal contributions in human genetics," observes Dr. Scherer. "We can look at the genome with binoculars right now. We will be able to resequence genomes soon and may be able to make disease-causing genes benign in the next decade. And this is going to revolutionize everything."