

The University of Toronto as a World Leader in Medical Genetics: Past, Present and Future

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Over the last 50 years, the use of genetics in medicine has undergone a vast transformation. While formerly having a very limited clinical application, such as the diagnosis and assessment of rare disorders, it has since blossomed into a field of research full of great promise. The University of Toronto has played a number of important roles in this transformation, including work in Muscular Dystrophy, Cystic Fibrosis, Alzheimer's Disease, genetics of the human immune system, and most recently, mapping chromosome 7 as part of the Human Genome project.

Duchenne Muscular Dystrophy (DMD) is the most common and devastating of the muscular dystrophies, affecting 1 in 3500 male newborns. It is a lethal X-linked genetic disease, and affected individuals will usually present with muscle weakness around age 3, lose the ability to walk by age 13, and do not usually survive beyond their early 20's, dying as a result of respiratory or cardiac failure.

For decades, this disease frustrated researchers and clinicians until 1983 when the DMD gene was mapped to a specific region on the short arm of the X chromosome. This significant breakthrough became the starting block in a race to identify and clone the DMD gene. The two established front-runners in this race were a research group at Harvard University Medical School and a group at the Hospital for Sick Children in Toronto headed by Dr. Ronald Worton. Throughout the mid-1980s, the two groups kept pace and both were able to successfully clone various segments of DNA from the X chromosome where the DMD gene is located. In 1987, both groups crossed the finish line. Both the Toronto and Harvard lab reported cloning the complete DMD complementary DNA (representing the complete DMD gene transcript) in parallel, but by using different molecular techniques.^{1,2} Unfortunately for the Toronto group, the team from Boston seems to have been given popular credit for having "discovered" the DMD gene even though both groups produced the same results at almost the same time.

The Boston group went on to isolate and characterize the gene product, a protein known as dystrophin. The Toronto team is

credited with much of the subsequent DMD gene mutational analysis which established that over 70% of DMD cases are due to either deletions within the gene or complete or partial duplications of the gene.³ In turn, this information paved the way for the development of methods used in prenatal diagnosis as well as methods to identify potential carriers of the disease.

The University of Toronto also played a critical role in generating the knowledge currently fuelling Cystic Fibrosis (CF) research. Clinical research examining family histories for CF first appeared in 1946 and indicated that the disorder was genetic in nature and probably due to a single recessive gene.

In the early 1980's, a major biochemical defect in patients affected with CF was uncovered. The discovery that organs affected by CF have epithelial tissue impermeable to chloride ions led to the measurement of chloride ion concentration in perspiration, a procedure that became the new cornerstone for diagnosing CF. As the studies of chloride ion impermeability progressed, many research groups engaged in a quest to find the gene responsible for this phenomenon. In 1989, a collaborative effort led by Drs. Lap-Chee Tsui and John Riordan at the Hospital for Sick Children and by Dr. Francis Collins at the Howard Hughes Medical Institute at the University of Michigan announced that the target gene had been isolated. The protein product from this gene was named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) because of its role in chloride ion transport.⁴

While identifying the gene, the team also found an abnormality that resulted in the loss of a single phenylalanine residue that accounted for up to 70% of all CF cases. Toronto's leading role in this discovery has resulted in multiple studies and the identification of many other mutations of the gene.⁴ Toronto researchers have also identified how CFTR interacts in the cell to transport chloride ions and they have suggested several options for treating Cystic Fibrosis.

Since these discoveries of the 1980's, genetic research in Toronto has continued to be prolific. Recent work in the field of Alzheimer's Disease has helped to solidify the University of

Toronto's reputation as a major international force in medical genetics. Alzheimer's Disease is a neurodegenerative disorder characterized by progressive memory and cognition loss. It is accompanied by physical changes in the brain such as loss of neurons, deposits of extracellular amyloid plaques and "tangles" of fibres between neurons. Epidemiological and molecular genetic data suggests that although there are likely multiple factors influencing the cause of Alzheimer's, genetic factors play a prominent role.

At the University of Toronto's Centre for Research in Neurodegenerative Diseases, Dr. Peter St. George-Hyslop, Director of the Centre, and his team have received international acclaim for their work in the genetics of neurological diseases. In 1995, they identified and cloned two defective genes known as presenilin 1 and 2 that accounted for familial early-onset Alzheimer's Disease.⁵ Linkage analysis mapped the loci for the two genes to chromosomes 14 and 1, respectively. Mutations in the presenilins cause Alzheimer's Disease by inducing abnormal processing of the β -amyloid precursor protein and the accumulation of a toxic derivative, amyloid-peptide, in patient's brains.

According to a study published in September 7, 2000 issue of Nature magazine, Dr. St. George-Hyslop's research group has found a completely unknown protein, nicastrin, that regulates presenilin-mediated production of the amyloid β -peptide.⁶ More importantly, they discovered a way to manipulate nicastrin to regulate the production of the harmful amyloid β -peptide. This research could ultimately lead to new drug treatments that could significantly improve the lives of Alzheimer's patients.

In addition to cloning genes responsible for specific diseases, researchers at University of Toronto have also played an integral role in cloning genes of crucial importance to the body's immune system. In 1984, a group led by Dr. Tak Mak at the Ontario Cancer Institute succeeded in cloning and sequencing the genes coding for the β -chain of the T-cell receptor molecule.⁷ Dr. Mak's group was able to isolate and clone mRNA from a human leukaemic T-cell line, and then to exploit key differences between B- and T-cells in order to determine which clones coded for the T-cell receptor. The determined sequence predicted a protein structure very similar to that of the immunoglobulins produced by B-cells.⁷

The impact of Dr. Mak's genetic breakthrough has been far-reaching. As research in the biomedical sciences expands, researchers are becoming increasingly aware of the importance of the immune system in the etiology and pathogenesis of many diseases, both infectious and otherwise. T-cells mediate many immune processes, relying on the incredible diversity of their receptors to recognize infected cells. Advances in our understanding of T-cell receptor biology will likely impact on our understanding and treatment of innumerable conditions including cancer, autoimmune disorders and heart disease.

The field of medical genetics has evolved beyond simply iso-

lating and sequencing genes responsible for specific diseases. Today, most of the attention in the field of medical genetics is focused on the Human Genome Project, a joint international effort aimed at sequencing each of the approximately 30,000 human genes. Conceived in the mid-1980's, and formally started in 1990, the Human Genome Project has gone from virtual anonymity to celebrity status, often reaching the front pages of major international newspapers. Many scientists expect the findings from the project to revolutionize the diagnosis and treatment of genetic disorders, and eventually aid in unravelling the genetic components of common and complex disorders such as heart disease and cancer.

Dr. Lap-Chee Tsui, Head Geneticist at the Hospital for Sick Children, and his research group, leads Toronto's contribution to the Human Genome Project. They are attempting to construct a physical, genetic and transcription map of the "long arm" region (7q) of chromosome 7, which has been estimated to account for 5% of the human genome. Diseases potentially associated with abnormalities of chromosome 7 include cancers of the breast, ovaries, prostate and pancreas.⁸

Constructing a physical map of the chromosomes is an important stepping stone in genomic research, and Toronto's contribution on chromosome 7 is an essential part. The mapping data provided by the project will give scientists an invaluable tool in their quest to elucidate the regulatory mechanisms of gene expression in human biology.

Although the field of medical genetics has fostered many important discoveries in the past, we are only now beginning to realize its potential for changing both the research and clinical face of medicine, and ultimately changing the overall delivery of health care in society. As Dr. Lap-Chee Tsui contends, "Genomics is more than just sequencing. It is also understanding the function of genes, not just scientifically, but also [the] implications for society in the post-genomic era.

References

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