ANNUAL REPORT
2005/2006

THE HESS B. AND DIANE FINESTONE LABORATORY
IN MEMORY OF JACOB AND JENNY FINESTONE
http://www.mcgill.ca/finestone/

Submitted by: Dr. David S. Rosenblatt, Director

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The Hess B. and Diane Finestone Laboratory in Memory of Jacob and Jenny Finestone was established to promote the field of medical genetics at McGill University. Dr. David S. Rosenblatt has been Director of the laboratory since its inception. The laboratory was established with the help of an endowment to McGill University and funding is used to advance the academic goals of the Division of Medical Genetics in the Department of Medicine of the McGill University Health Centre (MUHC). As such, this report also serves as the Annual Report of the Division of Medical Genetics of the Department of Medicine of the MUHC. It is available on the Internet (**http://www.mcgill.ca/finestone)**. Since the University Division in Medicine also has included the Division at the Jewish General Hospital, this report also encompasses parts of that activity. Within the past few years, major advances have occurred with the creation of the Department of Medical Genetics at the Jewish General Hospital.

Highlights: Research

Dr. Ken Dewar and his group sequenced the entire 4 Mb genome of the human bacterial pathogen *Clostridium difficile*, in an attempt to understand its genome structure and virulence factors. This organism has been responsible for significance morbidity and mortality in Quebec hospitals.

Dr. Thomas Hudson and his laboratory played a prominent role in the International HapMap Consortium. The publication of this work represented a major international research accomplishment of 2005.

Dr. David Rosenblatt and his laboratory discovered the *MMACHC* gene responsible for the *cblC* form of combined homocystinuria and methylmalonic aciduria, the most common inborn error of vitamin B_{12} (cobalamin) metabolism.

Highlights: Awards

Dr. Thomas Hudson:

Investigator Award	Canadian Institute of Health Research July 2002-August 2007
Achievement of the Year in Healthcare	Maclean's magazine, December 2005
Award for Research in Immunology	Canadian Society for Allergy and Clinical Immunology, September 2005

Highlights: Teaching

Dr. Mary Ann Thomas completed her CCMG training in cytogenetics and has taken up a staff position in Medical Genetics at Calgary. Dr. Fatma Bastaki completed her RV year, successfully passed the examination of the Royal College of Physicians and Surgeons of Canada, and returned to a hospital position in Dubai. Dr. Teresa Rudkin decided to transfer from Medical Genetics in order to complete training in Family Medicine. Dr. Nicolas Ah Mew completed his RIV year and served as Chief Resident. Dr. Philippe Campeau completed his RIII year and served as Assistant Chief Resident. Dr. Maha Al-Awadi and Dr. Khalid Al-Thihli completed their RII year in the Medical Genetics residency as did Dr. Mouna Ben Amor.

Highlights: Clinical

After more than five years, the committee to search for a Program Director for medical genetics of the MUHC has actually met, and there are several highly competent applicants for the position.

The recruitment of Dr. Marc Tischkowitz has made a major contribution to both the basic and clinical areas of cancer genetics and general medical genetics. He is based at the Jewish General Hospital and began working in August 2005.

Clinical Statistics:

Suzanne Dufrasne, M.Ps, Psychologist:
Huntington Disease
Number of new patients seen: 20
Number of sessions: 40
Number of counselling phone calls: 68
Total cases seen: 128

Stephanie Fox, MSc, MS, Genetic Counsellor:
Hereditary Cancer Clinic:
Counselling as of September 6th, 2005

Number of new patients seen: 62
Number of follow-up patients seen: 46
(Number of counselling phone calls: 20)
Total cases seen: 108

Number of breast cancer cases: 50
Number of colon cancer cases: 38
Number of other cancer cases: 7
Number of hemochromatosis cases: 7
Number of other cases: 6
Total: 108

Predictive Testing for Huntington Disease:
Counselling as of January 2006
Number of counselling sessions for Huntington disease: 5
Number of results sessions for Huntington disease: 4

Laura Palma, MSc, Genetic Counsellor
Hereditary Cancer Clinic
Counselling as of July 4th, 2005
Total # **new** patient (NP) visits: 70
Total # **follow-up** (FU) patient visits: 45
115

Total # **follow-up** (FU) (letters only)*****: 10 ***** this applies to patients who were not seen in clinic for FU but received a FU results letter

Description of patient visits by type (total = 115)

Total # **breast** cancer cases: 64
Total # **colon** cancer cases: 22
Total # **breast AND colon** cases: 5
Total # **other cancer** cases: 4
Total # **other** cases******: 20
115

****** This includes counselling for other genetic conditions which may/may not predispose to cancer (e.g. Cowden syndrome, pheochromocytoma, hemochromatosis, MEN1, tuberous sclerosis etc.)

Prevention Clinic, Fridays (last Friday of every month), 1:00-4:00p.m.
Total # follow-up (FU) patients seen: 60

Research Interests and Accomplishments of Individual Members:

Dr. Eleanor Elstein has an active clinic, which evaluates inherited cardiac diseases as well as systemic genetic diseases that have cardiac manifestations.

Dr. Ken Dewar and his laboratory are using genomics technologies to study genome structure and variation. They are participating in an NIH funded project to develop SNP-based genetic mapping tools for the vervet monkey, and have begun a Genome Canada/Genome Quebec project to generate the corresponding genome wide physical map. Preliminary results demonstrate the ability to delineate chromosomal breakpoints and to identify vervet BAC clones associated with evolutionary recently derived centromeres and pericentromeric regions. The

group is also interested in understanding genome structure and virulence factors in the human bacterial pathogen *Clostridium difficile*, which led to the sequencing of the entire 4 Mb genome during the past year.

Dr. William Foulkes' interests continue to be focused on hereditary cancer, specifically breast, colorectal and prostate cancer. His main contribution in 2005 was to extend his work on the basal phenotype of BRCA1-related breast cancer. In addition, he published several papers on Lynch (HNPCC) syndrome, in collaboration with colleagues both in Montreal and overseas. He was the co-organiser of a major conference on hereditary breast and ovarian cancer that was held in Montreal in October 2005 (**www.hboc.ca**).

T. Mary Fujiwara has research interests which include the study of the distribution and maintenance of genetic variability, including deleterious alleles in well-defined populations, in particular, the Hutterite population of North America – an inbred population isolate. During the current reporting period, she continued collaborations on mapping Mendelian diseases, and further delineated the clinical variability of a cerebellar hypoplasia called disequilibrium syndrome. This work was done in collaboration with Kenneth Morgan, although he is not a co-author on all the publications. She also collaborates with Daniel Bichet (Hôpital Sacré-Coeur de Montréal) on a worldwide collection of families with nephrogenic or neurohypophyseal diabetes insipidus. During the current reporting period, they were invited to write a review for the *Journal of the American Society of Nephrology*.

Dr. Brian Gilfix and his team are focused on two main areas of research: 1) Homocysteine and its Metabolism/Inborn Errors of Metabolism (Homocystinuria)-they have a large cohort of patients in the Adult Genetics Clinical with homocystinuria. His team is using this opportunity to explore new treatments of homocystinuria and investigate the effect of elevated homocysteine on other risk factors for cardiovascular disease; 2) Development of Laboratory Methods in Molecular Diagnostics and HPLC-they are developing and implementing assays based on hybridization probes to replace standard assays based on restriction fragment length polymorphism used to genotype for single nucleotide polymorphisms in the clinical laboratory. The benefit of this is decreased net cost and faster turn-around-time.

Dr. Thomas Hudson directs the McGill University and Genome Quebec Innovation Centre which is the largest genomic and proteomic facility in Canada. As mentioned above, Dr. Hudson played a major role in the International Haplotype Map Consortium and received great recognition for this work. His laboratory also is heavily involved in the study of the genetics of common disease. Dr. Hudson is one of Canada's premier scientists.

Dr. Ken Morgan has research interests in population genetics, pedigree analysis, and genetic modelling. He leads a Genetic Analysis Group that participated in two Networks of Centres of Excellence programs: the Canadian Genetic Diseases Network (CGDN) and the Mathematics of Information Technology and Complex Systems. His group is involved in the genetic analysis of Mendelian and complex traits in humans and mice. Accomplishments related to human genetics include: 1) mapping Mendelian diseases in the Canadian Hutterite population with collaborators in Calgary and Winnipeg, and further clinical delineation of a cerebellar hypoplasia; 2)

collaboration with Alexey Pshezhetsky, Hôpital Ste-Justine, in mapping the locus for mucopolysaccharidosis IIIC (Sanfilippo syndrome); 3) former postdoc Loredo-Osti developed methodology for segregation analysis of a quantitative trait in sibships to find evidence for a major gene for urine calcium excretion in families ascertained for kidney stones, a collaboration with Alain Bonnardeaux, Hôpital Maisonneuve-Rosemont; 4) collaboration with David Rosenblatt and mentoring of his student, Jordan Lerner-Ellis, in mapping the locus for methylmalonic aciduria and homocystinuria, cblC type, and identification in mutations in the *MMACHC* gene; 5) collaboration with Susie Tenenhouse (Montreal Children's Hospital) and collaborators in Boston to identify mutations in the gene encoding a sodium-phosphate cotransporter that cause hereditary hypophosphatemic rickets with hypercalciuria.

Dr. David Rosenblatt and his laboratory continue to be the major international referral source for the diagnosis of patients with inherited disorders of folate and vitamin B_{12}. They are involved in studying the biochemical and molecular bases of these diseases. Jordan Lerner-Ellis, a Ph.D. student, succeeded in discovering the *MMACHC* gene responsible for combined homocystinuria and methylmalonic aciduria, the most common inborn error of vitamin B_{12} metabolism. This work was published in Nature Genetics and received considerable publicity. It has allowed for carrier detection and more rapid prenatal diagnosis in those families in which mutations are known. Emily Moras has discovered a novel mitochondrial protein binder for cobalamin. Abigail Gradinger has been looking at the frequency of mutations in the *MCEE* gene among patients with elevated excretion of methylmalonic acid.

Dr. Marc Tischkowitz took up a position in September 2005 as Assistant Professor in the Departments of Human Genetics and Oncology at McGill University Faculty of Medicine. Prior to his current post, Dr Tischkowitz was a Consultant (Attending Physician) in Clinical Genetics at the North East Thames Regional Genetics Unit, Great Ormond Street Hospital, UK. He has medical training in both Clinical Genetics and Medical Oncology and his primary interests are molecular studies of cancer predisposition genes and the clinical management of familial cancer predisposition syndromes. He has a strong scientific background, which he has built upon since his undergraduate years. From 1999 to 2002 he undertook a PhD on the chromosome breakage syndrome Fanconi anemia and through this he has developed an interest in DNA repair mechanisms. He is currently in the process of establishing a research group to undertake innovative and effective research in the field of hereditary predisposition to cancer.

Dr. Patricia Tonin has two major areas of research interest. The first involves the identification of genetic factors that are implicated in the development and/or progression of human epithelial ovarian cancer. The second involves the study of genetic factors that predispose to hereditary forms of beast cancer: 1) The Molecular study of Human Epithelial Ovarian Cancer-Our knowledge of the molecular events associated with the development and progression of epithelial ovarian cancer has been limited by the lack of a suitable model system. Also, since the disease is often diagnosed at a late stage when numerous complex chromosomal changes have already taken place, the early molecular events remain largely unknown. Deletions of chromosome 3p and 17q (distinct from the BRCA1 locus) are frequent events in ovarian tumours of epithelial origin. Dr. Tonin has shown deletions in low grade, early stage tumours and therefore has hypothesized that these chromosomal regions harbour tumour suppressor genes whose function

is lost early in the development and/or progression of ovarian cancer. The goals of the CIHR funded projects are to refine the localization and then clone the putative chromosome 3p and 17q tumour suppressor genes. Previously, her team published a deletion map of chromosome 3p deletions observed in a large series of epithelial ovarian tumours. In addition they are applying a candidate gene approach and have excluded known candidates, such as TGF-ß-RII. They described a chromosome 3 transcriptome based on the comparison of expression profiles of ovarian cancer cell lines with normal surface epithelial cells using high through put oligonucleotide expression microarrays. In this study they were able to establish the sensitivity of detection and show that subtle changes in gene copy number are detectable by microarray analysis. In an effort to characterize the putative TSG on chromosome 3p implicated in ovarian tumourigensis, they established the relationship between chromosome losses frequently associated with specific regions of the human genome (BRCA2 and 13q, TP53 and 17p, BRCA1 and 17q, and Xp11) with that of 3p regions lost in ovarian cancer. They established chromosome 3p loss occurs independently from TP53 mutagenesis. They reported a comprehensive analysis addressing the fidelity of expression microarrays, such as Affymetrix GeneChips®, showing that rigorous investigation of target sequences representing genes on these microarrays should be pursued prior to engaging in experiments of target genes. Most recently her team has begun to translate their findings to identify markers for epithelial ovarian cancers; 2) Breast Cancer Susceptibility Genes: BRCA1 and BRCA2-Hereditary breast cancer accounts for approximately 5% to 10% of all breast cancers and large majority of hereditary cancer families are attributed to germline mutations in BRCA1 and BRCA2, which confer an increased susceptibility to both breast and ovarian cancer. Dr. tonin and her team are continuing to further define the spectrum of mutations in the BRCA1 and BRCA2 cancer susceptibility genes in the French Canadian population of Quebec. Most recently they reported a new recurrent BRCA2 mutation in the French Canadian population at risk for hereditary breast and ovarian cancer and determined that it is likely identical by descent. This latest discovery has redefined mutation screening protocols and improved genetic testing, and consequently genetic counselling, for this population.

MEETINGS AND PRESENTATIONS

KEN DEWAR

April 22-2006 — 15th Annual Scientific Meeting of the Canadian Genetic Diseases Network, Saint-Sauveur, QC
Title: Genome sequencing and analysis of a Quebec isolate of *Clostridium difficile*

SUZANNE DUFRASNE

November 22, 2005 — Hôpital Ste-Justine / Université de Montréal
Predictive Testing for Huntington Disease
Module for Masters degree students in Genetic Counselling

WILLIAM FOULKES

September 19, 2005 — National Council of Jewish Women of Canada
Gelber Conference Centre, Montreal, QC
Title: Role of genetic factors in cancer & familial diseases

September 28, 2005 — CCMG 2005 Annual Meeting
Château Bromont, Bromont, QC
Title: Genetics of colorectal cancer: What's new?

October 12, 2005 — 10th McGill International Symposium on Reproductive Endocrinology & Infertility and Women's Health Centre Mont-Royal, Montreal, QC
Title: Genetic influence of breast and gynecological cancers in pre-menopausal women

October 20, 2005 — First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes
BRCA: Today & Tomorrow
Marriott Château Champlain, Montreal, QC
Title: Overview - 10 years of BRCA1 and BRCA2
Title: Outcome following BRCA1/2 related breast cancer

February 2, 2006 — 5th International From Gene to Cure Congress Vrije Universiteit Amsterdam, Amsterdam, Netherlands
Title: Genetic Risk Assessment &
Title: Prevention of Hereditary Breast Cancer

STEPHANIE FOX

September 29-October 2, 2005	CAGC annual meeting (Canadian Association of Genetic Counsellors) Montreal, Quebec
October 20-21, 2005	First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes Presented workshop: Taking a history for cancer risk Montreal, Quebec
November 12-15, 2005	NSGC annual meeting (National Society of Genetic Counsellors) Los Angeles, California

BRIAN GILFIX

November 29, 2005	Montreal General Hospital
November 30, 2005	Royal Victoria Hospital Medical Grand Rounds **Title**: A mini-symposium on the gene that rusts

THOMAS HUDSON

August 12, 2005	Club Kiwanis Chicoutimi, QC **Title**: Medical Genetics: progress and hopes
September 20, 2005	Conference: From Biobanks to Biomarkers: Translating the Potential of Human Population Genetics Research to Improve the quality of Health of the EU Citizen, Hinxton, Cambridge, UK, **Title**: Unraveling the causes of chronic diseases
December 6, 2005	Guest speaker: Council of Community-Based Pediaticians, CME Meeting **Title**: Genetics for pediatricians
December 20, 2005	Invited speaker: The National Sciences Foundation of China, Beijing **Title**: From haplotypes to chronic diseases: the power of international consortia

KENNETH MORGAN

March 30-31, 2006	**Title**: First Canadian genetic epidemiology and statistical genetics workshop Member of organizing committee and co-chairman Toronto, ON

LAURA PALMA

September 29-October 2, 2005	CAGC annual meeting (Canadian Association of Genetic Counsellors) Montreal, Quebec Member of local organizing committee
October 20-21, 2005	First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes Presented workshop: Taking a history for cancer risk Montreal, Quebec
November 12-15, 2005	NSGC annual meeting (National Society of Genetic Counsellors) Los Angeles, California **Poster presentation** Perceived adequacy of social support and decisional conflict in prenatal screening for Down syndrome: An exploratory study Palma L**,** Shuman S, Goia G, Pierre-Louis J, Chitayat D, Kaiser A.

DAVID ROSENBLATT

September 18-23, 2005	Gordon Research Conferences **Discussion Leader**: B_{12} in medicine and toxicology Queen's College Oxford, England
Feb 15-16, 2006	Banbury Conference Long Island, Cold Spring Harbor.
March 6, 2006	MUHC-Montreal Children's Hospital Research Institute Research Seminar **Title**: What's new in the genetics of vitamin B_{12}? Montreal Children's Hospital

MARK TISCHKOWITZ

October 20, 2005	First International Symposium on the Hereditary Breast and Ovarian Cancer Susceptibility Genes BRCA: today & tomorrow Marriott Château Champlain, Montreal, QC

PATRICIA N. TONIN

January 13, 2006	Montreal Children's Hospital **Topic**: Towards the identification of chromosome 3p tumour suppressor genes implicated in ovarian cancer Seminar

ORIGINAL PUBLICATIONS

Anderson SK, **Dewar K**, Goulet ML, Leveque G, Makrigiannis AP. Complete elucidation of a minimal class I MHC natural killer cell receptor haplotype. *Genes Immun.* 2005 Sep; 6(6): 481-92.

Arcand SL, Provencher D, Mes-Masson A-M, **Tonin PN**. 2005 OGG1 Cys^{326} variant, allelic imbalance of chromosome band 3p25.3 and TP53 mutations in ovarian cancer. *Int J Oncol.* 5:1315-20.

Arnes JB, Brunet JS, Stefansson I, Begin LR, **Wong N**, Chappuis PO, Akslen LA, **Foulkes WD**. Placental cadherin and the basal epithelial phenotype of BRCA1-related breast cancer. *Clin Cancer Res.* 11(11): 4003-11, 2005.

Belanger H., Beaulieu P., Moreau C., Labuda D., **Hudson T.J.,** Sinnett D. Functional promoter SNPs in cell cycle checkpoint genes. *Hum Molec Genet.* 14:2641-8, 2005.

Boycott, K.M., S. Flavelle, A. Bureau, H.C. Glass, **T.M. Fujiwara**, E. Wirrell, K. Davey, A.E. Chudley, J.N. Scott, D.R. McLeod, and J.S. Parboosingh: Homozygous deletion of the very low density lipoprotein receptor gene causes autosomal recessive cerebellar hypoplasia with cerebral gyral simplification. *Am J Hum Genet.* 77:477-483, 2005.

Callén E, Casado JA, **Tischkowitz MD**, Bueren JA, Creus A, Marcos R, Dasí A, Estella JM, Muñoz A, Ortega JJ, de Winter J, Joenje H, Schindler D, Hanenberg H, Hodgson SV, Mathew CG, Surrallés J. A common founder mutation in FANCA underlies the world highest prevalence of Fanconi anemia in Gypsy families from Spain. *Blood* 2005 Mar 1; 105(5): 1946-9.

Caron, J., **Loredo-Osti J.C.**, **Morgan K.**, Malo D. Mapping of interactions and mouse congenic strains identified novel epistatic QTLs controlling the persistence of *Salmonella enteritidis* in mice. *Genes Immun.* 6:500-508, 2005.

Chappuis PO, Donato E, Goffin JR, **Wong N**, Begin LR, Kapusta LR, Brunet JS, Porter P, **Foulkes WD**. Cyclin E expression in breast cancer: predicting germline BRCA1 mutations, prognosis and response to treatment. *Ann Oncol*. 16 (5): 735-742, 2005.

Coelho JJ, Arnold A, Naylor J, **Tischkowitz M**, MacKay J. An assessment of the efficacy of cancer genetic counseling using real-time videoconferencing technology (Telemedicine) compared to face-to-face consultations. *Eur J Cancer.* 2005 41 (15): 2257-2261.

Collett K, Stefansson IM, Eide J, Braaten A, Wang H, Eide GE, Thoresen SO, **Foulkes WD**, Akslen LA. A Basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. *Cancer Epidemiol Biomarkers Prev.* 14 (5): 1108-12, 2005.

Croteau S., Roquis D., Charron M.C., Frappier D., Yavin D., **Loredo-Osti J.C.**, **Hudson T.J.,** Naumova A.K. (2005). Increased plasticity of genomic imprinting of Dlk1 in brain is due to genetic and epigenetic factors. *Mamm Gen.* Feb; 16(2): 127-35, 2005.

Cullinane CA, Lubinski J, Neuhausen SL, Ghadirian P, Lynch HT, Isaacs C, Weber B, Moller P, Offit K, Kim-Sing C, Friedman E, Randall S, Pasini B, Ainsworth P, Gershoni-Baruch R, **Foulkes WD**, Klijn J, Tung N, Rennert G, Olopade O, Couch F, Wagner T, Olsson H, Sun P, Weitzel JN, Narod SA. Effect of pregnancy as a risk factor for breast cancer in BRCA1/BRCA2 mutation carriers. *Int J Cancer.* 117 (6): 988-91, 2005.

Denarier E., Forghani R., Farhadi H., Dib S., Dionne N., Friedman H., Lepage P., **Hudson T.J.**, Drouin R., Peterson A.C. Functional organization of a Schwann cell enhancer. *J Neurosc.* Nov 30; 25(48): 11210-7, 2005.

Desrosiers, M.-P., Kielczewska A., **Loredo-Osti J.C.**, Girard Adam S., Makrigiannis A.P., Lemieux S., Pham T., Lodoen M.B., **Morgan K.**, Lanier L.L., Vidal S.M. Epistasis between mouse *Klra* and major histocompatibility complex class I loci is associated with a new mechanism of natural killer cell-mediated innate resistance to cytomegalovirus infection. *Nat Genet.* 37:593-599, 2005.

Eisen A, Lubinski J, Klijn J, Moller P, Lynch HT, Offit K, Weber B, Rebbeck T, Neuhausen SL, Ghadirian P, **Foulkes WD**, Gershoni-Baruch R, Friedman E, Rennert G, Wagner T, Isaacs C, Kim-Sing C, Ainsworth P, Sun P, Narod SA. Breast cancer risk following bilateral oophorectomy in BRCA1 and BRCA2 mutation carriers: an international case-control study. *J Clin Oncol.* 23 (30): 7491-6, 2005.

Ernest S, **Hosack A**, O'Brien WE, **Rosenblatt DS**, and Nadeau JH: Homocysteine levels in A/J and C57BL/6J mice: genetic, diet, gender, and parental effects. *Physiol Genom.* 21(3): 404-410, 2005.

Ferrier DE, **Dewar K**, Cook A, Chang JL, Hill-Force A, Amemiya C. The chordate ParaHox cluster. *Curr Biol.* 2005 Oct 25; 15(20): R820-2.

Florez J.C., C.M. Agapakis, P. Burtt, M. Sun, P. Almgren, L. Rästam, T. Tuomi, D.Gaudet, **T. J. Hudson,** M. J. Daly, K. G. Ardlie, J. N. Hirschhorn, L. Groop and D. Altshuler (2005). Association testing of the protein tyrosine phosphatase 1B gene (PTPN1) with type 2 diabetes in 7,883 people. *Diabetes.* 54(6): 1884-91.

Foulkes WD, **Hamel N**, Oros KK, **Tonin PN.** 2005. Double heterozygosity and founder mutations in BRCA1/2 in women with ductal carcinoma in situ. JAMA. 294:553-4 [Letter to the editor].

Frosk, P.F., Greenberg C.R., Tennese A.A.P., Lamont R., Nylen E., Hirst C., Frappier D., Roslin N.M., Zaik M., Bushby K., Straub V., Zatz M., de Paula F., **Morgan K.**, **Fujiwara T.M.**, and Wrogemann K.W.: The most common mutation in *FKRP* causing limb girdle muscular dystrophy type 2I (LGMD2I) may have occurred only once and is present in Hutterite and other populations. *Hum Mutat.* 25:38-44, 2005.

Ge B., Gurd S., Gaudin T., Dore C., Lepage P., Harmsen E., **Hudson T.J.**, **Pastinen T**. Survey of allelic expression using EST mining. *Genome Res.* Nov 15:1584-91, 2005.

Gilfix BM. Vitamin B_{12} and Homocysteine. *CMAJ.* 2005; 173(11): 1360.

Glass, H.C., Boycott K.M, Adams C., Barlow K., Scott J.N., Chudley A.E., **Fujiwara T.M.**, **Morgan K.**, Wirrell E., McLeod D.R.: Autosomal recessive cerebellar hypoplasia in the Hutterite population. *Develop Med Child Neurol.* 47:691-695, 2005.

Guigonis V, Frémeaux-Bacchi V, Giraudier S, Favier R, Borderie D, Massy Z, Mougenot, **Rosenblatt DS**, and Deschênes G: Late-onset thrombocytic microangiopathy caused by *cblC* disease: Associated with a factor H mutation. *Am J Kidney Dis.* 45(3): 588-595, 2005.

Hamet P., Merlo E., Seda O., Broeckel U., Tremblay J., Kaldunski M., Gaudet D., Bouchard G, Deslauriers B., Gagnon F., Antoniol G., Pausova Z., Labuda M, Jomphe M, Gossard F., Tremblay G., Kirova R., Tonellato P., Orlov S.N., Pintos J., Platko J., **Hudson T.J.,** Rioux J.D., Kotchen T.A., Cowley A.W. Quantitative founder-effect analysis of French Canadian families identifies specific Loci contributing to metabolic phenotypes of hypertension. *Am J Hum Genet*. 2005 May; 76(5): 815-32. Epub 2005 Mar 30.

Honrado E, Osorio A, Palacios J, Milne RL, Sanchez L, Diez O, Cazorla A, Syrjakoski K, Huntsman D, Heikkila P, Lerma E, Kallioniemi A, Rivas C, **Foulkes WD**, Nevanlinna H, Benitez J. Immunohistochemical expression of DNA repair proteins in familial breast cancer differentiate BRCA2-associated tumors. *J Clin Oncol.* 23 (30): 7503-11, 2005.

International HapMap Consortium, (**Hudson TJ**, co-author). A haplotype map of the human genome. *Nature.* Oct 437:1299-320, 2005.

Kotsopoulos J, Lubinski J, Lynch HT, Neuhausen SL, Ghadirian P, Isaacs C, Weber B, Kim-Sing C, **Foulkes WD**, Gershoni-Baruch R, Ainsworth P, Friedman E, Daly M, Garber JE, Karlan B, Olopade OI, Tung N, Saal HM, Eisen A, Osborne M, Olsson H, Gilchrist D, Sun P, Narod SA. Age at menarche and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Cancer Causes Cont.* 16 (6): 667-674, 2005.

Kotsopoulos J**,** Olopado OI**,** Ghadirian P**,** Lubinski J**,** Lynch HT**,** Isaacs C**,** Weber B**,** Kim-Sing C**,** Ainsworth P**, Foulkes WD,** Eisen A**,** Sun P**,** Narod SA**.** Changes in body weight and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res.* 7 (5): R833-R843, 2005.

Laflamme, N, Giroux S, **Loredo-Osti JC**, Elfassihi L, Dodin S, Blanchet C, **Morgan K**, Giguère V, Rousseau F: A frequent regulatory variant of the estrogen-related receptor alpha gene associated with BMD in French-Canadian premenopausal women. *J Bone Mineral. Res* 20:938-944, 2005.

Lamont, R, **Loredo-Osti JC**, Roslin NM, Mauthe J, Coghlan G, Nylen E, Frappier D, Innes AM, Lemire EG, Lowry RB, Greenberg CR, Triggs-Raine BL, M**organ K**, Wrogemann K, **Fujiwara TM**, Zelinski T. A locus for Bowen-Conradi syndrome maps to chromosome region 12p13.3. *Am J Med Genet.* 132A: 136-143, 2005.

Lincoln M.R., **Montpetit A**, Cader MC, Saarela J, Dyment DA, Tiislar M, Ferretti V, Tienari PJ, Sadovnick AD, Peltonen L, Ebers CG, **Hudson TJ**. A predominant role for the HLA class II region in the association of the MHC region with multiple sclerosis. *Nat Genet.* 37:1108-12, 2005.

Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S**, Dewar K**, **Hudson TJ**, Horn R, Rene P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005 Dec 8; 353(23): 2442-9. Epub 2005 Dec 1.

Loredo-Osti, JC, Roslin NM, Tessier J, **Fujiwara TM**, **Morgan K**, Bonnardeaux A. Segregation of urine calcium excretion in families ascertained for nephrolithiasis: Evidence for a major gene. *Kidney Int.* 68:966-971, 2005.

Makrigiannis AP, Patel D, Goulet M-L, **Dewar K**, Anderson SK. Direct Sequence Comparison of Two Divergent Class I MHC Natural Killer Cell Receptor Haplotypes. *Genes Immun.* 6: 71-83, 2005.

Makriyianni I, Hamel N, Ward S, **Foulkes WD**, Graw S. BRCA1:185delAG found in the San Luis Valley probably originated in a Jewish founder. *J Med Gene.* 42 (5): e27, 2005 (WDF is corresponding author).

McVety S**,** Younan R**,** Li L**,** Gordon PH**, Wong N**, **Foulkes WD,** Chong G**.** Novel genomic insertion-- deletion in MLH1: possible mechanistic role for non-homologous end-joining DNA repair. *Clin Genet.* 68 (3): 234-238, 2005.

Morel CF, Scott P, Christensen E, **Rosenblatt DS**, Rozen R: Prenatal diagnosis for severe methylenetetrahydrofolate reductase deficiency by linkage analysis and enzymatic assay. *Mol Genet Metab*. 85(2): 115-120, 2005.

Morel CF, **Watkins D**, Scott P, Rinaldo P, **Rosenblatt DS**: Prenatal diagnosis for methylmalonic acidemia and inborn errors of vitamin B_{12} metabolism and transport. *Mol Genet Metab.* 86:160-171, 2005.

Morgan NV, Essop F, Demuth I, de Ravel T, Jansen S, **Tischkowitz M**, Lewis CM, Wainwright L, Poole J, Joenje H, Digweed M, Krause A, Mathew CG. A common Fanconi anaemia mutation in Black populations of Sub-Saharan Africa. *Blood.* 1; 105(9): 3542-4, 2005.

New HV, Cale CM, **Tischkowitz M**, Flores De Laurnaga B, Jones A, Telfer P, Veys P, D'Andrea A, Mathew CG, Hann I. Nijmegen breakage syndrome diagnosed as Fanconi anaemia. *Pediatr Blood Cancer*. 44(5): 494-9, 2005.

Nusbaum C, Zody MC, Borowsky ML, Kamal M, Kodira CD, Taylor TD, Whittaker CA, Chang JL, Cuomo CA, **Dewar K**, FitzGerald MG, Yang X, Abouelleil A, Allen NR, Anderson S, Bloom T, Bugalter B, Butler J, Cook A, DeCaprio D, Engels R, Garber M, Gnirke A, Hafez N, Hall JL, Norman CH, Itoh T, Jaffe DB, Kuroki Y, Lehoczky J, Lui A, Macdonald P, Mauceli E, Mikkelsen TS, Naylor JW, Nicol R, Nguyen C, Noguchi H, O'Leary SB, O'Neill K, Piqani B, Smith CL, Talamas JA, Topham K, Totoki Y, Toyoda A, Wain HM, Young SK, Zeng Q, Zimmer AR, Fujiyama A, Hattori M, Birren BW, Sakaki Y, Lander ES. DNA sequence and analysis of human chromosome 18. *Nature*. 2005 Sep 22; 437(7058): 551-5. Erratum in: *Nature*. 2005 Dec 1; 438(7068): 696. O'Neill, Keith [added].

Ouellet V, Provencher DM, Maugard CM, Le Page C, Ren F, Ren F, Lussier C, Novak J, Ge B, **Hudson TJ**, **Tonin PN**, Mes-Masson A-M. 2005. Discrimination between serous low malignant potential and invasive epithelial ovarian tumors using molecular profiling. Oncogene. 24: 4672-87.

Pastinen T, Ge B, Gurd S, Gaudin T, Dore C, Lemire M, Lepage P, Harmsen E and **Hudson TJ.** Mapping common regulatory variants to human haplotypes. *Hum Molec Genet.* 2005 Dec 15; 14(24): 3963-71. Epub 2005 Nov 21.

Pausova Z, Gaudet D, Gossard F, Bernard M, Kaldunski ML, Jomphe M, Tremblay J, **Hudson TJ**, Bouchard G, Kotchen TA, Cowley AW, Hamet P. Genome-wide scan for linkage to obesity-associated hypertension in French Canadians. *Hypertension*. Dec; 46: 1280 – 1285, 2005.

Poon AH, Laprise C, **Lemire M**, **Hudson TJ**, Schurr E. NRAMP1 is not associated with asthma, atopy, and serum immunoglobulin E levels in the French Canadian population. *Genes Immun*. 6(6): 519-27, 2005.

Presneau N, **Dewar K**, Forgetta V, Provencher D, Mes-Masson A-M, **Tonin PN**. 2005. Loss of heterozygosity and transcriptome analyses of a 1.2 Mb candidate ovarian cancer tumor suppressor locus region at 17q25.1-q25.2 *Mol Carcinog*. 43: 141-54.

Presneau N, Shen Z, Provencher D, Mes-Masson A-M, **Tonin PN**. 2005. Identification of novel variant, 1484delG in the 3'UTR of *H3F3B*, a member of the histone 3B replacement family, in ovarian tumors. *Int J Oncol*. 26: 1621-27.

Qu H, Bharaj B, Liu XQ, Curtis JA, Newhook LA, Paterson AD, **Hudson TJ**, Polychronakos C. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. *Nat Genet.* 2005 Feb; 37(2): 111-2, 2005.

Qu H, Tessier MC, **Hudson TJ**, Polychronakos C. Confirmation of the association of the R620W polymorphism in the protein tyrosine phosphatase PTPN22 with type 1 diabetes in a family based study. *J Med Genet.* 2005 Mar; 42(3): 266-270, 2005.

Rosel PE, Forgetta V, **Dewar K**. (2005). Isolation and characterization of twelve polymorphic microsatellite markers in bottlenose dolphins (*Tursiops truncatus*). *Molec. Ecology Notes* (in press).

Saba T, Montpetit A, Verner A, Rioux P, **Hudson TJ**, Drouin R, Drouin C. An atypical form of erythrokeratodermia variabilis maps to chromosome 7q22. *Hum Genet.* Feb; 116(3): 167-71, 2005. Epub 2004 Nov 25.

Serre D, Nadon R & **Hudson TJ**. Large-scale recombination rate patterns are conserved among human populations. *Genome Res.* Nov 15; 1547-1552, 2005.

Su Z, Segura M, **Morgan K**, **Loredo-Osti JC**, Stevenson MM. Impairment of protective immunity to blood-stage malaria by concurrent nematode infection. *Infec Immun.*73:3531-3539, 2005.

Sun S, Greenwood CM, Thiffault I, **Hamel N**, Chong G, **Foulkes WD**. The HNPCC associated MSH2*1906G-->C founder mutation probably originated between 1440 CE and 1715 CE in the Ashkenazi Jewish population. *J Med Genet.* 42 (10): 766-768, 2005.

Tessier M-C, Qu H, Fréchette R, Bacot F, Grabs R, Taback SP, Lawson M, Kirsch S, **Hudson TJ**, Polychronakos C. Type 1 diabetes and the OAS gene cluster: association with splicing polymorphism or haplotype? *J Med Genet.* 2005 July 13; [Epub ahead of print].

Tonin PN, Forgetta V, Provencher D, Presneau N, Mes-Masson A-M, **Dewar K**. (2005) Loss of heterozygosity and transcriptome analysesof a 1.2 Mb candidate ovarian cancer tumor suppressor locus region at 17q25.1-q25.2. *Molec Carcinogen.* (In press).

van der Klift H, Wijnen J, Wagner A, Verkuilen P, Tops C, Otway R, Kohonen-Corish M, Vasen H, Oliani C, Barana D, Moller P, Delozier-Blanchet C, Hutter P, **Foulkes WD**, Lynch H, Burn J, Moslein G, Fodde R. Molecular characterization of the spectrum of genomic deletions in the mismatch repair genes MSH2, MLH1, MSH6, and PMS2 responsible for hereditary nonpolyposis colorectal cancer (HNPCC). *Genes Chromos Cancer.* 44 (2): 123-38, 2005.

Weitzel JN, Robson M, Pasini B, Manoukian S, Stoppa-Lyonnet D, Lynch HT, McLennan J, **Foulkes WD**, Wagner T, Tung N, Ghadirian P, Olopade O, Isaacs C, Kim-Sing C, Moller P, Neuhausen SL, Metcalfe K, Sun P, Narod SA. A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev.* 14 (6): 1534-8, 2005.

Winckler W, Graham RR, de Bakker PI, Sun M, Almgren P, Tuomi T, Gaudet D, **Hudson TJ**, Ardlie KG, Daly MJ, Hirschhorn JN, Groop L, Altshuler D. Association testing of variants in the hepatocyte nuclear factor 4{alpha} gene with risk of type 2 diabetes in 7,883 people. *Diabet.* Mar 54(3): 886-92, 2005.

Winckler W, Burtt NP, Holmkvist J, Cervin C, de Bakker PI, Sun M, Almgre P, Tuomi T, Gaudet D, **Hudson TJ**, Ardlie KG, Daly MJ, Hirschhorn JN, Altshuler D, Groop L. Association of common variation in the HNF1 alpha gene region with risk of type 2 diabetes. *Diabet.* 54: 2336-42, 2005.

Xu J, Dimitrov L, Chang BL, Adams TS, Turner AR, Meyers DA, Eeles RA, Easton DF, **Foulkes WD**, Simard J, Giles GG, Hopper JL, Mahle L, Moller P, Bishop T, Evans C, Edwards S, Meitz J, Bullock S, Hope Q, Hsieh CL, Halpern J, Balise RN, Oakley-Girvan I, Whittemore AS, Ewing CM, Gielzak M, Isaacs SD, Walsh PC, Wiley KE, Isaacs WB, Thibodeau SN, McDonnell SK, Cunningham JM, Zarfas KE, Hebbring S,Schaid DJ, Friedrichsen DM, Deutsch K, Kolb S, Badzioch M, Jarvik GP, Janer M, Hood L, Ostrander EA, Stanford JL, Lange EM, Beebe-Dimmer JL, Mohai CE, Cooney KA, Ikonen T, Baffoe-Bonnie A, Fredriksson H, Matikainen MP, Tammela TLj, Bailey-Wilson J, Schleutker J, Maier C, Herkommer K, Hoegel JJ, Vogel W, Paiss T, Wiklund F, Emanuelsson M, Stenman E, Jonsson BA, Gronberg H, Camp NJ, Farnham J, Cannon-Albright LA, Seminara D; ACTANE Consortium. A combined genomewide linkage scan of 1,233 families for prostate cancer-susceptibility genes conducted by the international consortium for prostate cancer genetics. *Am J Hum Genet.* 77 (2): 219-29, 2005.

Yotova V, Labuda D, Zietkiewicz E, Gehl D, Lovell A, Lefebvre JF, Bourgeois S, Lemieux-Blanchard E, Labuda M, Vezina H, Houde L, Tremblay M, Toupance B, Heyer E, **Hudson TJ**, Laberge C. Anatomy of a founder effect: myotonic dystrophy in Northeastern Quebec. *Hum Genet*.117: 177-87, 2005.

Zauber NP, Sabbath-Solitare M, Marotta S, Zauber AG, **Foulkes WD**, Chan M, Turner F, Bishop DT. Clinical and genetic findings in an Ashkenazi Jewish population with colorectal neoplasms. *Cancer.* 15: 104 (4): 719-29, 2005.

RESEARCH OPERATING FUNDS – 2005-2006

AGENCY

Dewar, Ken	Genome Canada/Genome Quebec, Group Grant – 2001-2005 National Institutes of Health - (P.I.) - 2004-2008
Foulkes, William	FRSQ – Group Grant – 2000-2005 Valorisation-Recherche Quebec – Group Grant – 2002-2006 Montreal Breast Cancer Foundation – Group Grant – 2003-2006 US Army – Group Grant – 2003-2006 CIHR – Co-PI – 2003-2007
Hudson, Thomas	Canadian Foundation for Innovation, Co-Applicant – 2005-2007 Canadian Foundation for Innovation, Infrastructure Grant - Project Leader – 2002-2006 Canadian Foundation for Innovation, Co-Investigator – 2004-2007 Genome Canada - PI – 2006-2008 CIHR, Operating Grant – PI - 2001-2006 CIHR – Operating Grant – 2003-2008 Juvenile Diabetes Foundation International, Group Grant – 2001-2006 Genome Canada – PI, 2006-2009 Ontario Genomics Institute/Genome Quebec – PL – 2001-2005 Genome Canada/Genome Quebec – Group Grant – 2001-2005 CIHR - Group Grant – 2001-2006 Valorisation-Recherche Quebec – Group Grant – 2002-2006 Burroughs Wellcome Fund, PI – 2002-2007 CIHR – Operating Grant – 2002-2005 National Institute of Allergy & Infectious Diseases – Co-investigator – 2004-2009 Networks of Centres of Excellence – Leader Theme I, 2005-2007 European Commission – Co-investigator – 2006-2008
Morgan, Kenneth	Networks of Centres of Excellence, Operating– Investigator, 1999-2009 CIHR – Investigator, Group grant – 2003-2008 CIHR, Co-applicant, 2003-2006 NSERC - Postdoctoral Fellowship to Fabrice Larribe, 2004-2005
Rosenblatt, David S.	CIHR – Operating – 2001-2006 (PI) March of Dimes – Operating – 2001-2005 (PI) Garrod Association– Operating – 2004-2005 (PI)

Tischkowitz, Mark	CFI, Leaders Opportunity Fund, March 2006
Tonin, Patricia N.	CRS – Co-investigator – Strategic Grant - 2005-2007 CIHR – Co-investigator – Operating – 2005-2008 Quebec Breast Cancer Foundation – Co-investigator - Group-operating 2004-2007 CIHR – Co-investigator – Operating Grant –2004-2006 FRSQ –Co-investigator – Operating-Group – 2000-2007 Valorisation-Recherche Québec – co-investigator – Operating Group –2002-2006 CFI – Co-investigator – Infrastructure – 2002-2006 Montreal Breast Cancer Foundation – Co-investigator – Operating Group – 2003-2006 CIHR – Operating Grant – Collaborator – 2002-2005 Cancer Research Society – Co-PI – 2002-2005 CIHR – Infrastructure – 2002-2005 CFI – Infrastructure/Innovation Grant – Investigator – 2000-2005 CIHR – Operating – PI – 2002-2006

FINANCIAL REPORT – 2005/2006

Starting Balance		**$ 83,487**
Salary Support and Benefits (Brunet, Dufrasne, Karim, Lavoie, Veyre, Yamani)	$ 68,460	
Conferences, Seminars, & Travel	$ 14,958	
Library & Membership	$ 4,776	
Material & Supplies	$ 2,076	
Minor Equipment	$ 8,902	
Miscellaneous	$ 1,767	
Professional Fees	$ 1,185	
Total Expenses		**$ 102,124**
Balance		**$ (18,637)**