Prospective Graduate Student Handbook 2015

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www.hg.med.umich.edu
A Letter From Our Chair

Welcome to the Department of Human Genetics!

I am delighted that you are interested in our program for pursuit of your degree. Graduate education and research are the most important parts of our department mission. The relationship between a student and their mentor is a very special one. I encourage you to meet and get to know our faculty and become familiar with their diverse research interests in the broad field of genetics and genomics as you seek to identify the best mentor and project. Our faculty takes great pride in their trainees as they master the ability to conduct independent research, present their work orally, and publish it.

Our graduates pursue a variety of careers in academia, government, biotechnology and other areas. No matter what your job turns out to be, the abilities you gain in graduate school will apply. These include the ability to pose a question and to design a way to address it, to think critically about data, to lead a project and function independently, and to be a life-long learner. Being a graduate student is an intensive apprenticeship and different in many ways from undergraduate education. The focus shifts from absorbing what is known to learning how it was discovered, what the evidence is for it and how sound that evidence is, and where gaps in knowledge exist. Research at a lab bench, a computer, or in the clinic, requires the awakening of your curiosity, the development of an independent and questioning spirit, and a commitment of time. As you invest in developing these skills you will be rewarded with the thrill of discovery and confidence that grows from your accomplishments. I look forward to hearing about your research projects as they evolve, and I hope that you will keep in touch with us after you graduate and establish your career.

You are invited to participate fully in department events and activities. Our annual retreat, September 18-19, 2015, will be held at the Kellogg Biological Station at Gull Lake. This is an excellent opportunity to meet faculty, senior graduate students, and postdoctoral fellows who can become members of your professional network.

Students are expected to attend and participate in department activities throughout the year. Our seminar series (http://www.hg.med.umich.edu/seminars) includes invited speakers from University of Michigan and other institutions who are doing cutting edge research in genetics and genomics. As graduate students you will have the opportunity to meet with these speakers and get input on your research, discuss their presentation, and hear about their career path. Challenge yourself to develop a question for each speaker! Our M.S. and Ph.D. students present research from the literature on Wednesdays at noon and their progress in research on Fridays from 4-5 pm, typically in Buhl 5915. Please come, not just to support your colleagues, but also to learn about new scientific discoveries published by other geneticists around the world and those that may be happening right down the hall. These forums are also intended to encourage questions and scientific interaction. The more engaged you are, the more you will learn.

Please feel free to contact any of our faculty, senior students, and administrative staff if you have questions or need assistance. All of us are listed on the website with our contact information: http://www.hg.med.umich.edu/. Multiple perspectives can help when making important decisions. In particular, I invite you to contact Irene Park and Owen Funk as they are willing to serve as additional mentors and/or are student representatives for the department this year. JoAnn Sekiguchi is Director of Graduate Studies; her office door is always open to help handle student issues. Karen Grahl is our student services representative.

In closing, I hope you have a terrific semester, and I’m looking forward to getting to know you.

Sincerely,

Sally A. Camper, Ph.D.
James V. Neel Professor and Chair
Admissions Process
To be recruited to the Ph.D. program, you must complete an application to the Program in Biomedical Sciences (PIBS). All highly qualified applicants are interviewed. Based upon the interview and application data, the Admissions Committee makes offers to the highest ranking applicants. It is the policy of PIBS to strive for an adequate representation of underrepresented minorities in its graduate programs.

Departmental Overview
Individuals who demonstrate mastery of knowledge in human genetics and contribute substantial and original scientific knowledge to the field will earn a Doctor of Philosophy (Ph.D.) degree in Human Genetics. The program of study leading to a Ph.D. degree normally requires 4-6 years beyond a Bachelor of Science (B.S.) degree. The first two years of the program are occupied with course work and hands-on research experiences. Once a student passes the Preliminary Examination and successfully completes course work and research rotations, he or she will become a Candidate for the Ph.D. degree in Human Genetics.

The final 2-4 years of the doctoral program are spent primarily on original scientific research. In the normal course of events, a student will choose both a research mentor at the end of the first year and full doctoral thesis committee by the end of the second year. To receive the Ph.D. degree, each doctoral student is required to write a thesis, representing a substantial and original contribution to the field of human genetics, and defend the thesis before his or her committee.

Academic Curriculum
Ph.D. students usually complete three major courses (~3 credits each) during each semester of their first year and at least one major course during each semester of their second year. Additionally, students participate in several seminar courses (1-2 credits each) during each of their first two years. For semester dates and details, see the current Rackham Graduate School Academic Calendar. Specific course requirements are flexible. Students should select courses based on their interests and previous educational experiences. Since students will have diverse interests and career goals, it is expected and encouraged that they diversify their course elections. Counseling on course options will be provided through a variety of mechanisms. Current Human Genetics students are a valuable source.

Laboratory Rotations
Each Ph.D. student is required to complete a minimum of two laboratory rotations with different faculty members. The purposes of these experiences are to allow the student to choose a research mentor/laboratory for their thesis research and to expose the student to multiple methods of research inquiry, areas of research investigation, and technology. The timing of rotations should correspond to fall, winter and spring terms.

Teaching Experience
A semester of teaching is a valuable part of our Ph.D. program experience. It is recommended that students obtain one semester of teaching experience. The timing is flexible. A variety of teaching opportunities are available in the Department of Human Genetics via core graduate courses and in the Department of Biology via undergraduate courses and laboratory sections. The Department of Biology application deadline for fall/winter semester Graduate Student Instructor (GSI) positions is March/November.

Preliminary Examination
The Preliminary Examination is an oral exam given in early May at the end of the second year. The purpose of the oral examination is to allow students to demonstrate their ability to think critically and to design experiments that will test hypotheses and contribute to the understanding of basic genetic principles. Each student is expected to choose from a list of topics in an area of research that is unrelated to both the research program of their mentor’s laboratory and their own anticipated Ph.D. thesis research. Each student will prepare a 10 page written research proposal according to standard grant format: Abstract, Specific Aims, Biological Significance, and Experimental Design. In order to help students recognize the level of detail and type of material that is appropriate to include in each of these grant sections, a few examples of successful Postdoctoral Research Applications are available for review. The emphasis of the oral examination that follows the submission of the written proposal is for students to realize they need not be familiar with all of the experimental details of the techniques they have proposed to use, but be familiar with the limitations and potential pitfalls of the techniques they have proposed to use.
**Thesis Committees**

Once a student has achieved Candidacy for the Ph.D. degree, he/she will select a thesis committee that will be chaired by the research mentor. The committee must consist of at least 2 faculty members from the Department of Human Genetics (in addition to the chairperson) and at least one “cognate” faculty member from another department. Most committees include a total of 5 faculty members. The student should meet with his/her thesis committee for the first time no later than January of the third year and then once every six to nine months. Students should view the thesis committee as a resource. Students should not wait until they have “good data” to show the committee. The committee can be of greatest assistance in addressing research problems. In addition, thesis committee members are an important source of support for the student’s future professional life.

**Departmental Events**

The Department of Human Genetics sponsors a seminar series of external speakers, short courses with several speakers on a related theme, and a weekly trainee research seminar. There are a variety of informal special interest groups that offer opportunities for students to present research results. We have a departmental retreat in the fall, which provides an opportunity for students and faculty to get to know one another. Research is presented in the form of posters and short talks.

**Financial Support**

The Department is committed to providing continuous, equitable support to all students in the Human Genetics Ph.D. program. Currently this includes two terms of tuition coverage per year, a health care program, and an annual stipend. Throughout the duration of the doctoral program, students are encouraged to apply for outside funding through a variety of training grants and fellowships, e.g., from the National Institutes of Health (NIH), National Science Foundation (NSF), or Howard Hughes Medical Institute. For a comprehensive list of training grants and programs available to students in Human Genetics, see [http://medicine.umich.edu/medschool/education/phd-programs/about-pibs/funding-benefits](http://medicine.umich.edu/medschool/education/phd-programs/about-pibs/funding-benefits).

**Health Care Coverage**

GradCare is a program designed for University of Michigan graduate students to provide year round health care. GradCare is administered by UM Premier Care, a health care provider for University faculty and staff. The full cost of student health care coverage is paid by the Department and is not deducted from the graduate student’s stipend. A student’s spouse and children can be covered at no additional charge. Students and their families can select primary care physicians from an extensive directory of local providers. Full coverage is provided for many services including: one annual eye exam, surgery, ambulatory emergency care, and maternity care. A small co-pay is charged to the student for routine office visits and prescription drugs.

In addition to health care coverage, Delta Dental of Michigan provides dental coverage for all eligible University of Michigan graduate students. You can choose from three dental plan options. All three options provide coverage for preventive care and orthodontic services.

**Living in Ann Arbor**

Ann Arbor, located along the scenic Huron River valley, is a residential town with a permanent population of about 114,000 and a student population of approximately 44,000 University of Michigan students. The U-M was established at its Ann Arbor location in 1837, where it has enjoyed a long and rich history. The University possesses dozens of libraries, museums, and learning and computing centers. The U-M Medical Center is one of the largest and most progressive health care facilities in the country. The city and the campus are geographically intertwined with pockets of shops, restaurants, and businesses. University and community recreational events, concerts, theater, dance, art, film societies, and other seasonal events are plentiful. Lecture series from many University departments are open to the public. The University encompasses many student organizations, athletic and recreational services, performance groups, political/social activism organizations, and special interest groups. Ann Arbor has a history of active political expression and as soon as an address is established, students may register to vote. The popular U-M spectator sports offer reduced ticket prices to students. The Department of Recreational Sports provides an assortment of activities and intramural sports at five drop-in facilities. Additionally, the city offers a variety of recreational facilities including swimming pools, ice rinks, parks, bike trails, canoe rentals, tennis courts and basketball courts. The Great Lakes provide excellent day-trip excursions, and Chicago and Toronto offer wonderful weekend trips.

To learn more about living in Ann Arbor, visit the websites listed below. They include information about the best places to eat, annual festivals, the locations of important city departments and anything else you might need to know about the area.

- Visit Ann Arbor: [http://www.annarbor.org](http://www.annarbor.org)
- Arbor Web: [http://arborweb.com/](http://arborweb.com/)
- Main Street Ann Arbor: [http://mainstreetannarbor.org](http://mainstreetannarbor.org/)
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The major focus of our research is on the development and diseases of the peripheral nervous system, which is composed of motor and sensory neurons and myelinating Schwann cells.

Exploring the role of aminoacyl-tRNA synthetases in neurodegenerative disease:

Aminoacyl-tRNA synthetases (ARSs) are a ubiquitously expressed, essential class of enzymes responsible for charging tRNA molecules with their cognate amino acids. We have identified mutations in the glycyl-tRNA synthetase gene (GARS, which encodes the enzyme that ligates glycine to tRNAGly molecules) in patients with two axonal peripheral neuropathies: Charcot-Marie-Tooth disease type 2D (CMT2D) and distal spinal muscular atrophy type V (dSMA-V). These findings raised immediate interest in how mutations in a ubiquitously expressed gene could lead to the limited phenotype of peripheral neuropathy. Functional analyses of GARS mutations have shown that the majority are associated with a loss of function when modeled in the yeast ortholog (GRS1). Furthermore, wild-type GARS becomes associated with granular structures present in cultured neurons and human peripheral nerve axons, while the majority of mutated forms of GARS do not; these results also suggest a loss-of-function mechanism for GARS mutations. One possible explanation for the axon-specific phenotype of CMT2D and dSMA-V is that disease-associated mutations interfere with tRNA charging, thus affecting axonal protein synthesis. In support of this, mutations in the tyrosyl-tRNA synthetase gene (YARS) have been implicated in another variant of peripheral neuropathy, and a mutation in the alanyl-tRNA synthetase gene (Aars) has been found in a mouse model of ataxia. Combined, these data suggest that ARSs have an important role in normal neuronal function. We are testing this hypothesis by: (1) Screening all 37 human ARS genes in patients with peripheral neuropathy and no known mutation; and (2) Characterizing the role of GARS in neurons using cellular and proteomic approaches.

Defining transcriptional hierarchies important for Schwann cell development:

The SRY-box containing 10 (SOX10) transcription factor has a critical role in the development and function of neural crest derivatives, including melanocytes, enteric neurons, and Schwann cells. Not surprisingly, mutations in the SOX10 gene are associated with a number of neural-crest-related phenotypes, including demyelinating peripheral neuropathy. Underscoring the importance of SOX10 in Schwann cell function are the findings that certain genes directly regulated by SOX10 (e.g., those encoding myelin protein zero [MPZ] and connexin 32 [CX32]) are frequently mutated in patients with demyelinating peripheral neuropathy. We are interested in identifying other loci regulated by SOX10 in Schwann cells. Toward this we are: (1) Computationally identifying highly-conserved SOX10 consensus sequences in the human genome; (2) Testing the surrounding genomic segments for enhancer activity in cultured Schwann cells; and (3) Identifying nearby loci that are expressed in Schwann cells. These loci, and the associated regulatory elements, will subsequently be evaluated for a role in demyelinating peripheral neuropathy.

Selected Publications


Our research interests focus on identifying genetic causes of neurodevelopmental disorders and understanding the resulting cell and molecular mechanisms of disease. Modeling pathology not only informs us about disease mechanisms, but also sheds light on novel features of normal brain development. A major challenge to understanding human neurodevelopmental disorders has been the lack of affected tissue. However, the recent addition of induced pluripotent stem cells (iPSC) to the human disease modeling toolbox has the potential to greatly expand our understanding of human disease mechanisms. Well-characterized, human based modeling systems, are also an invaluable resource for interpreting the clinical significance of deleterious alleles and human genomic variation.

Selected Publications


Dr. Boyle’s research group aims to combine both computational and wet lab strategies to answer questions related to the transcriptional regulatory control of human genes. We believe that a complex regulatory control determines the fates of individual non-coding regulatory elements and that the integration of diverse genetic, epigenetic, and disease data is the best way to explore this control. Using innovative computational and wet lab approaches the lab both characterizes the function of these regulatory elements as well as examines the effect of genetic variation in these regions.

Selected Publications


The Burke Laboratory research effort is concentrated in three main areas: (1) the analysis of the stability of gene expression during mammalian aging, (2) quantitative trait locus (QTL) analysis of complex, multigenic traits in the laboratory mouse, and (3) the development of engineering systems for microfluidic analysis.

The first research area seeks to understand the genetic mechanisms involved in stabilizing adult gene expression in late-life. We are testing the hypothesis that aging-dependent reactivation is a general phenomenon of transcriptionally repressed genes. Two types of genes show this unusual expression: (1) genes on the non-pseudoautosomal X chromosome in females (X inactivation), and (2) genes that are differentially expressed based on parent of origin (genomic imprinting). In both epigenetic control systems, we detect a loss of precision with increasing age. We are also measuring the stability of the messenger RNA alternative splicing process during normal aging.

The second research area, in a collaborative effort with Dr. Richard Miller (University of Michigan, Institute of Gerontology and Department of Pathology) and other investigators at the University of Michigan, is a long-term project to identify regions of the mouse genome correlated with inter-individual variation in aging phenotypes. Several phenotypic indicators of aging are being examined in parallel, including T-cell populations, circulating hormones, bone structure, late-life hearing loss, and cancer incidence. We have identified gene locations associated with several late-life phenotypes, using a reproducible, genetically heterogeneous laboratory mouse population (UM-HET). The third project is a collaborative effort with Dr. Mark Burns (University of Michigan, Department of Chemical Engineering), and is developing a high-throughput DNA genotype analysis system that can be provided to genetics researchers at low cost. The microfluidic devices will: a) require human interaction only for initial loading of samples, b) provide consistent experimental processing and quality control, c) decrease sample processing time and human labor, d) reduce reagent costs by reducing the genotyping biochemistry to nanoliter volumes, and e) be fully controlled by integrated circuitry.

Selected Publications


My laboratory’s research is aimed at finding genes involved in neurological and psychiatric diseases as well as behavior in general. We use genetic methodologies and have identified specific single gene mutations that cause ataxia, seizures and behavioral abnormalities in mice and humans. Our ataxia research takes a genomic approach, including linkage, homozygosity, next generation sequencing, gene expression and machine learning network analysis. We have identified several ataxia genes and use mouse and zebrafish as models to further verify and analyze the genes and protein products.

In contrast to Mendelian single gene defects, human behavior and risk for psychiatric illnesses such as depression and alcoholism are determined by a complex interaction of environmental and multiple genetic risk factors. We include environmental factors and quantitative differences and development in our analyses, and collaborate extensively with clinicians and biostatisticians. We have shown that some genetic effects depend strongly on the environment.

Selected Publications


Genetics of Birth Defects: neuroendocrine, auditory, and skeletal development. We use two main approaches in our birth defects research - sequencing patient DNA to identify novel disease genes and use of cell culture and animal models, especially the mouse, to understand the mechanism and pathophysiology of disease. Genetically engineered mice that model human disease are also valuable for testing therapeutic interventions. We are particularly interested in the genetic control of differentiation and cell proliferation that pertains to stem cells, progenitors and specialized cells. We study transcriptional regulation, cell signaling, and the interaction of these.

Selected Publications


*corresponding author featured on the cover.

Dr. Carethers' research interests include familial cancer and polyposis syndromes, mechanisms of tumor progression, tumor genetics, tumor markers, DNA mismatch repair, molecular pathology, and colorectal cancer disparities.

Selected Publications


Carethers JM, Koi M, Tseng-Rogenski SS. EMAST is a Form of Microsatellite Instability That is Initiated by Inflammation and Modulates Colorectal Cancer Progression. Genes (Basel). 2015 Mar 31;6(2):185-205. doi: 10.3390/genes6020185. Review. PMID: 25836926


In the Cheung lab, we focus on human genetics and study gene regulation. We combine computational and experimental methods to study normal variation in human traits and genetics of complex diseases. We assess the extent of individual differences in cellular phenotypes such as gene expression and organelle function. Then, we treat the variable phenotypes as quantitative traits to map and characterize molecularly their regulators. We are particularly interested in regulators that affect transcription and RNA processing. Our studies focus on normal human cells at baseline homeostatic states; however, we are also interested in cellular responses to stress including DNA damage, protein load and metabolic perturbations. By studying regulation in normal cells, we gain insights into how dysregulations lead to diseases. While our interest is in human biology, recently, we have taken advantage of yeast genetics to complement our studies.

Our rotation and thesis projects integrate experimental and analytical approaches to study basic regulatory mechanisms. Besides identifying regulators, we strive to understand how regulators interact to maintain cellular functions and respond to stress. Most of our study involves gene mapping, deep sequencing of nucleic acids and molecular studies to gain a better understanding of not only the functions of individual genes and proteins but also how genes and their pathways are coordinated.

Selected Publications


Most ordinary traits and common diseases in humans are heritable. In fact, the genetic bases of many traits and diseases from height to breast cancer to longevity have been recognized for nearly a hundred years. However, it is only recently that we have had the tools and resources required to search for their genetic underpinnings.

The goal of the Douglas lab is to apply, adapt, and develop a variety of statistical and computational tools and contemporary resources to identify the genetic contributions to medically important traits and common diseases in human populations. For example, a major, current aim in the lab is to discover the genetic factors that influence breast density, the third strongest risk factor for breast cancer, after age and mutations in the BRCA1 and BRCA2 genes.

Because most medically important traits like breast density are complex, being influenced by an inter-play of both genetic and non-genetics factors, study design is critically important. To this end and in an effort understand the genetic basis of breast density, we recently recruited and characterized a sample of approximately 1,500 Amish women with respect to multiple breast cancer risk factors, including breast density. One of the advantages of studying the Amish is that they have unique cultural and reproductive behaviors that reduce the effect of non-genetic factors – such as delayed childbearing and the use of contraceptives and female hormones – that affect breast density.

Selected Publications

Shah KP, Douglas JA (2013) A method to prioritize quantitative traits and individuals for sequencing in family-based studies. PLOS ONE 8:e62545


Molecular analysis of human cancer pathogenesis; β-catenin-dependent Wnt signaling; transgenic and knockout mouse models of colorectal cancer; miRNAs and cancer; CDX2 homeobox gene function; factors and mechanisms regulating tissue stem cells and cell fate determination in intestinal epithelium.

The research in the Fearon laboratory seeks to address the means by which specific oncogene and tumor suppressor gene defects contribute to the pathogenesis of colon and other cancers and to develop novel strategies for early detection and treatment of colorectal adenomas and carcinomas.

**Selected Publications**


Genetics of Vascular Remodeling, and Interactions between Hematologic and Vascular Traits

Blood vessels respond to injury and various hemodynamic and metabolic stimuli by changing physiologic properties or mechanical properties such as diameter and wall thickness. This process of structural adaptation, known as vascular remodeling, may improve vascular function or may cause adverse effects, such as occlusion of blood flow, promotion of thrombotic events, or aneurysm and rupture of the blood vessel. My laboratory is focused on the genetics of vascular remodeling as it pertains to the development of common diseases, such as atherosclerosis and hypertension, as well as rare diseases such as fibromuscular dysplasia, which causes stroke and severe hypertension in children and adults. We are also studying interactions between blood traits and these same diseases. We use traditional and cutting-edge genetic methods to discover associations, and my laboratory is carrying these findings forward to functional, mechanistic studies using molecular genetic and vascular biology techniques, including ex vivo and in vivo models of disease. We are seeking students with an interest in human genetics, molecular genetics or vascular biology as it pertains to the biologic basis of complex cardiovascular diseases.

Selected Publications


MID: 21356094.


Precise control of the blood-clotting system is essential for maintenance of the circulation in all higher animals. Deficient function of this system can lead to fatal bleeding following even a minor injury, whereas overactivity of this system can produce unwanted blood clots, resulting in blockages to critical blood vessels, as occurs in such diseases as heart attack and stroke.

We study the molecular genetics of blood clotting, specifically von Willebrand factor, coagulation factor V and plasminogen activation. See:
http://www.hhmi.org/research/investigators/ginsburg.html
http://lsi.umich.edu/facultyresearch/labs/ginsburg

Selected Publications


Our research focuses on the areas of genome instability and the molecular biology of human genetic disease. A longstanding interest is the study of chromosomal fragile sites. These are chromosome loci that are especially sensitive to breakage following replication stress. Our studies of fragile sites have led to our current focus on copy number variants (CNVs). In only the last few years, thousands of normal CNVs spanning tens to hundreds of kb have been found in the human genome where they play important roles in normal variation and evolution. In addition, spontaneous or de novo CNVs are a major cause of genetic and developmental disorders, including mental retardation, autism, schizophrenia, epilepsy, skeletal defects and many others. Despite their importance, there is limited understanding of how most CNVs arise and the risk factors involved. We have found that replication stress, like that leading to fragile site breaks, creates CNVs in human cells. Our current efforts are focused on expanding on these findings to identify the genetic and environmental factors involved in CNVs formation using novel assays and high-resolution genome analysis approaches.

Our second major interest is Hutchinson-Gilford Progeria (HGP). HGP is characterized by the premature onset of many of the features associated with aging, such as an aged appearance and arteriosclerosis, with death usually before age 15. We were involved in a consortium effort that identified the gene (lamin A/C) responsible for this fascinating disorder, opening the door to functional studies and the identification of therapeutic drug trials. Our current interests include the role of lamin A in genome stability and the identification of genes responsible for related progeroid disorders.

**Selected Publications**


Glynn MW, **Glover TW**: Incomplete processing of mutant lamin A in Hutchinson-Gilford progeria leads to nuclear abnormalities, which are reversed by farnesyltransferase inhibition. Hum Mol Genet 14: 2959-2969, 2005.


Research Interest:

Spermatogenesis is a complex process requiring extensive changes in the chromatin and epigenetic landscape for proper specification and differentiation. Aberrations in this process can lead to infertility, a major health problem worldwide, affecting 1 in every 8 couples. Approximately 50% of the infertility cases lack a clear etiology, and this is attributed, in part, to the poor understanding of the basic signaling, genetic, and epigenetic mechanisms regulating fertility. To find a treatment, one needs to understand the normal developmental process. To achieve this goal the Hammoud laboratory will emphasize on two areas summarized below:

1) In-vitro gametogenesis:

Spermatogenesis requires a complex integration of intrinsic/extrinsic factors to execute the full/normal developmental process. Here, we aim to use high throughput genomics to define intrinsic and extrinsic (niche) factors that maybe important for maintaining spermatogenesis both in-vivo and/or in-vitro. A greater understanding of the normal gametogenesis process will provide a foundation for understanding how changes either in microenvironment or germ cell can lead to male infertility. Reconstitution of this process in-vitro either from pre-pubertal/adult germ stem cells or through the use of induced pluripotent stem cells will be transform the lives of many individuals.

2) Epigenomic Engineering and transgenerational inheritance:

The Cas9/Crispr and Talen technologies have revolutionized the feasibility of genetic/epigenetic engineering. The lab aims to utilize modified genetic engineering strategies to address the role of epimutations on fertility and transgenerational inheritance.

Selected Publications:


Early Post-Implantation Mammalian Body Patterning

Post-implantation development requires precisely coordinated cellular movements in preparation for gastrulation. We have characterized and genetically mapped a spontaneous X-linked mouse mutant, Polypodia (Ppd), which we discovered and established as a mutant line using in vitro fertilization and genetic crosses to explore early post-implantation body plan patterning. Ppd mice exhibit ectopic caudal limbs and other extraordinary malformations, which has been observed in humans and other animals. We hypothesize that Ppd alters vertebrate patterning during pregastrulation or early gastrulation stages by changing expression of patterning genes in the post-implantation embryo. Because of the strikingly similar malformations of Ppd mice by comparison with embryos treated with exogenous retinoic acid at E4.5-E5.5, we hypothesize that Ppd malformations are secondary to alterations of primitive streak formation or mesodermal cell allocation via premature activation of retinoic acid synthesis or alterations of Wnt/β-catenin signaling. We are determining the timing and nature of lethality and testing for alterations in post-implantation gene expression using RNA probes for genes expressed in the primitive streak and proximal epiblast and overlying visceral endoderm; distal visceral endoderm; extraembryonic ectoderm; and epiblast. To determine whether induced alterations in gene expression occur in common between Ppd and RA-treated mice, we are comparing RA-treated pregnant wild-type mouse embryos at E4.5 - E5.5 to Ppd mutant mice. We are studying the functional consequences of the mutation using transgenic mice and other tools.

Long-range Transcriptional Regulation of Hoxa13 in Developing Limbs and the Urogenital Tract

While we have learned a great deal about the underlying roles of many transcription factors in developmental fate and in human malformations, we know less about how such genes are targeted for expression in selected tissues at specific times and abundance. Proper regulation of such aspects occurs via cis elements, located within those genes or more often at great genomic distances away, as well as by trans-acting factors bound to those elements in multiprotein complexes. However, many questions remain as to how these elements are used mechanistically.

Hoxa13 is a critical Hox transcription factor in the development of distal limbs and the genitourinary tract. We recently published data showing that three genes, Hibadh, Taxbp1, and Jazf1, upstream of Hoxa13 and the Hoxa cluster, together with Hoxa13 and Evx1 constitute a domain of 5 genes, which we call the HEHTJ domain, that appear to be coordinately expressed during murine limb and genital bud development. We also reported the enhancer capabilities of a highly conserved 2.25 kb sequence (mmA13CNS) 300 kb upstream of the HoxA cluster in transgenic mice. Our long-term goals are to determine the mechanisms that govern transcriptional regulation of the Hoxa13 gene in limbs and genitourinary structures in the larger context of the HEHTJ domain. The proximity of a highly conserved cluster of Hox genes and coordinately regulated upstream genes offers novel opportunities to study enhancer regulatory mechanisms.

Specifically, we are 1) using BAC transgenesis to capture enhancers for HEHTJ gene expression; and 2) working to identify cis-acting sequences necessary for Hoxa13 expression in mouse tissues. We created mice transgenic for a two BACs encompassing mmA13CNS and have shown the existence of at least two enhancers for proper expression in murine limbs and genital bud development. We are also making a Hoxa13 gene/β-globin lacZ reporter linked to candidate enhancers derived from our BAC transgene work. The plan is to introduce these constructs into the Hoxa13 null background to test for rescue of in utero lethality, limb and urogenital malformation in Hoxa13 -/- embryos.

Selected Publications


Our goal is to elucidate chromatin regulatory mechanisms engaged in cognitive development and function with a focus on intellectual disabilities (ID). These studies may lay a foundation for amelioration of cognitive deficits and will likely contribute to a merging of chromatin biology and neuroscience.

ID imposes cognitive impairment on 1-3% of the total population. Patients are diagnosed by their low intelligence quotient (IQ). Human genetic studies have identified a plethora of candidate genes. Meanwhile, post-translational modifications of histones have been recognized as a “language” describing a variety of nuclear events. Intriguingly, more than 20 ID gene products can be assigned to be regulators of histone/DNA modification network. Accurate interpretation of the histone modification network, therefore, appears to be required for proper cognitive function. However, little is known about how these mutations lead to intellectual disabilities. ID thus is a good pathological model for investigation of the roles of histone/DNA modifications. Our primary focus is on chromatin regulators mutated in ID.

**Selected Publications**


Our research aims to define the epigenetic mechanisms that regulate X-chromosome inactivation, which results in transcriptional silencing of most genes along one of the two X-chromosomes in female mammals.

Please see the lab website for additional details. http://www-personal.umich.edu/~kalantry/Kalantry_Lab/Welcome.html

Selected Publications


The focus of the research in my laboratory is to understand the developmental pathways that are required for formation of the caudal portion of the embryo and the mechanisms that lead to birth defects affecting caudal structures in humans.

There are 2 major projects currently ongoing in the laboratory:

1. Mechanisms leading to the caudal regression phenotype in adrenocortical dysplasia (acd) mice.

Caudal regression syndrome (CRS) is a birth defect of the caudal region that is characterized by premature truncation of the vertebral column along with urogenital tract malformations. The etiology of CRS is unknown, but it is clinically very heterogeneous and likely has multiple etiologies. My laboratory studies the adrenocortical dysplasia (acd) mouse as a model for caudal regression syndrome. acd is a recessively inherited mouse mutation that causes embryonic lethality on certain genetic strains. The acd mouse was initially described as a model for human congenital adrenal hypoplasia, as the predominant defects in adult mice include adrenal insufficiency and reduced survival. We previously characterized a striking embryologic phenotype in acd mice that consists of caudal truncation, vertebral defects, and limb anomalies, resembling CRS in humans. The gene that is mutated in acd mice encodes a telomere protein named TPP1, which is a component of the shelterin telomere complex. Shelterin functions as a cap that protects telomeres from being recognized and processed by the DNA repair machinery and regulates telomerase access to telomeres. Consistent with the known function of TPP1 as a critical component of shelterin, cells from acd mutant mice exhibit evidence of telomere dysfunction and genomic instability. The role of telomere dysfunction in causing birth defects is unexplored; thus, the acd mouse is a unique model to study the mechanisms that lead to CRS, and the causative mechanisms are likely to be similar in humans. We are also interested in collecting patients with CRS phenotypes to potentially identify genetic etiologies of this disorder.

We are interested in pursuing the following questions:

1) What is the mechanism by which the acd mutation causes the CRS phenotype?
2) Why is the phenotype in acd mutant embryos restricted to the caudal region?
3) What is the role of telomere dysfunction and/or genomic instability in causing birth defects?
4) Are the underlying mechanisms the same for CRS that is caused by other genetic or environmental etiologies?

2. Genetic and genomic analysis in patients with cloacal exstrophy (OEIS complex).

Another focus of my laboratory is the identification of new genes that are required for proper formation of the caudal region of the embryo. To accomplish this goal, we are collecting samples from human patients with cloacal exstrophy (also called OEIS complex omphalocele, exstrophy of the bladder, imperforate anus, spinal defects), which is a sporadic condition that includes defects of the bladder, bowel, and genital region in humans. The cause of cloacal exstrophy is unknown, but it is thought to involve improper migration of specific groups of cells during formation of the bladder, bowel and genital structures in the embryo. We are currently performing both genetic and genomic analyses to identify causative genes for this condition.

Selected Publications


We apply a genome-wide approach to understanding the processes that shape the structure, content, and sequence variation of genomes among human populations and between species. We seek to understand how biological and historic population processes act to shape genomic variation and how this variation leads to the wide range of phenotypic diversity observed in the natural world.

We take a genomics approach that involves high-throughput sequencing and genotyping with population-genetic modeling. We apply genomics approaches to address questions related to the biology of genomes in a range of systems including humans, non-human primates, and domestic dogs.

Selected Publications


We develop genome-scale technologies to comprehensively identify sequence variants, resolve genomic structures, and dissect their functional impacts with respect to molecular and cellular phenotypes. These efforts fall into two major areas:

1. Haplotype-resolved sequencing. We have developed new sequencing methods to experimentally resolve the haplotype phase of variants, which is almost entirely lost during standard short-read sequencing. We have leveraged phased genome sequencing to resolve the structures of normal and cancer genomes, and to enable the first non-invasive whole-genome sequencing of a human fetus. We are now pursuing refinements to scale this approach to large cohorts. In particular, we are interested in targeted phasing of individual loci, e.g., HLA genes.

2. Dissecting sequence-function relationships using saturation mutagenesis. The rate-limiting step in genetic research is shifting from variation discovery to functional interpretation. Similarly, clinical resequencing frequently uncovers variants lacking clear functional impacts, including many missense or non-coding mutations. We are developing new methods to dissect underlying sequence-function relationships, and to better distinguish pathogenic from benign mutations, by coupling saturation mutagenesis with functional selection using deep sequencing as a quantitative “read-out”. In this approach, we construct large allelic series, e.g., to include every possible amino acid substitution within a given protein. These are introduced en masse to cells in a tissue culture model, followed by functional selection to deplete (or enrich) cells carrying loss-of-function alleles. Using deep sequencing, abundances of every allele are measured both before and after selection, and the differences are taken as a measure of loss of function. We are initially applying this system to dissect the impacts of missense and regulatory mutations in DNA mismatch repair genes, which are implicated in a wide range of cancers. In the future, we expect this approach to be broadly applicable in identifying functional sites and cryptic regulatory mechanisms within disease-relevant genes and pathways.

Selected Publications


I am interested in identification of critical genes and proteins required for development and function of the auditory and vestibular systems, the interactions between these molecules, and the regulatory programs that control their expression. My laboratory uses both forward and reverse genetic approaches to evaluate the effects of mutations on inner function in the mouse. We use these approaches to better understand the nature of inherited hearing loss in humans, to characterize gene function, and to develop potential therapies to alleviate deafness and vestibular dysfunction. We are also using mouse models to investigate molecular pathways that may offer protection and/or repair of the auditory system in response to noise overstimulation, toxic drug exposures, or aging.

Selected Publications


Evolution of the cerebral cortex is thought to underlie our species’ most remarkable cognitive, perceptive, and motor capabilities, the execution of which depends on the precise establishment of axonal connectivity during development. Miswiring of cortical circuitry can lead to disorders, including autism and schizophrenia, that affect the most distinctly human cognitive functions.

Research in the Kwan laboratory is aimed at understanding the developmental processes that underlie cortical circuit assembly, their evolution during the emergence of human cognition, and their dysregulation in neurodevelopmental disorders. Our approach integrates: 1) human genetic and genomic studies to identify candidate genes; 2) neurobiological analyses of genetically-engineered mouse models and post-mortem human brains to characterize the roles of these genes in circuit development; and 3) investigations of their molecular interactions to dissect candidate pathways of normal and disordered neocortical development. Using this multispecies, interdisciplinary strategy, our research program is centered on two complementary themes:

1.) The first examines the fundamental mechanisms that control highly conserved aspects of neocortical circuit development using mouse genetics. The neocortex is a mammalian specific advance. The neocortical circuits that underlie fundamental functions such as conscious sensory perception and motor movement are well conserved across mammals and thus amenable to being modeled in the mouse. This line of pursuit includes the mechanisms that underlie the normal wiring of the corticospinal system, the collection of descending axons that enable voluntary movements in all mammals, and the potential of these mechanisms to be targeted for repair after injury.

2.) The second examines novel candidate mechanisms of human disorders of neocortical development. The emergence of higher cognitive functions in primates was accompanied by structural changes in the neocortex, including the acquisition of novel regional specializations such as the human Broca’s speech and language area. It has been hypothesized that these advances in neocortical organization and circuitry, while enabling higher cognition, may have also increased our species’ susceptibility to disorders that affect cognition. Leveraging a multispecies approach, we seek to unravel the molecular pathways most relevant to the development and dysfunction of the neural circuits in the human neocortex.

Further information can be found at www.kwanlab.org
The Li lab studies the genetic basis of complex human diseases using genomic approaches. Currently our interests include analyses of gene expression patterns in postmortem brain tissues associated with major depression, bipolar disorder, and schizophrenia, sequencing-based variant discovery and analysis in rare Mendelian disorders and the bipolar disorder, integrated analysis of cancer genome alterations, microbial dynamics in CF airways, and spontaneous mutations in the human genome.

Selected Publications


Our laboratory research focuses on the genetic basis of neural development and disorders of human development. Specifically, we focus on genes predicted to influence neuronal stem cell proliferation, differentiation, and migration. We are studying the roles of an ATP dependent chromodomain remodeling gene, Chd7, in the developing inner ear, olfactory system, and central nervous system. CHD7 is a mutated in CHARGE syndrome, a human congenital anomaly condition that affects the brain, eyes, ears, heart, and craniofacial structures. We use genetic approaches in mice to study how loss of CHD7 disrupts neuronal and organ development. We are specifically interested in epigenetic modification of gene expression by CHD7 and related chromatin remodelers, and how these modifications lead to phenotypic variability. We also participate in collaborative studies to better understand the genetic mechanisms of autism and other developmental disorders of the nervous system. Our studies have important implications for understanding the mechanisms involved in nervous system and other organ development, and for improving the diagnosis and treatment of these developmental disorders.

Selected Publications


Donna M. Martin, M.D., Ph.D.  
Donita B. Sullivan Research Professor of Pediatrics  
Professor of Human Genetics  
donnamm@umich.edu
We are studying neurological disease mutations in genes encoding human voltage-gated sodium channels and phosphoinositide metabolism. To examine the molecular mechanisms of pathogenesis, we generate mouse models of specific human mutations. We are screening patient populations to identify new disease mutations. In related projects, we are cloning several new mouse mutants, using genomic tools including human/mouse genomic sequence comparisons to identify noncoding regulatory sequences.

Selected Publications


Ferguson CJ, Lenk GM, Jones JM, Grant AE, Winters JJ, Dowling JJ, Giger RJ and Meisler MH (2012) Neuronal expression of Fig4 is necessary and sufficient to prevent spongiform neurodegeneration, Human Molecular Genetics 21: 3525- 3534. PMC3406753

Our research group is primarily focused on the analysis of whole genome sequence data to identify genetic variation (primarily structural variation) and examine their potential functional impact in disease phenotypes. We are particularly interested in analyzing complex regions of the genome that are not easily resolved through modern sequencing approaches and which may exhibit interesting mechanistic origins. We are also interested in the large-scale integration of genomic, expression, methylation and proteomic data sets, as well as the application of whole genome sequence analysis in clinical diagnostics.

Selected Publications


The goal of our laboratory is to understand how an abundant class of “jumping genes,” known as retrotransposable elements, impacts the structure and function of human genomes. In particular, we study Long INterspersed Element-1 (LINE-1 or L1) retrotransposons. The average human genome is estimated to contain roughly 80-100 LINE-1 elements that are able to mobilize (i.e., retrotranspose) to new genomic locations by a copy and paste mechanism termed target-site primed reverse transcription. On occasion, LINE-1 retrotransposition events can disrupt gene function and de novo LINE-1 insertions have led to sporadic cases of genetic disease. During the past decade, we have used genetic, molecular biological, biochemical, and genomic technologies to learn more about LINE-1 element biology. We currently are using these technologies to address the following questions: 1) How does L1 retrotranspose? 2) How do LINE-1 retrotransposition events impact the human genome? 3) How do cellular factors promote or restrict LINE-1 retrotransposition? 4) How does LINE-1 retrotransposition contribute to intra- and inter-individual genetic variation? We currently have openings for motivated graduate students and postdoctoral fellows who are interested in helping us answer the above questions.

Selected Publications


Why are 1 out of every 6 couples infertile?

When two XY species hybridize, why are the resultant males rare, absent or infertile?

These two apparently unrelated questions motivate our research, which is converging towards a common answer. Our laboratory addresses these questions by studying the genetic and molecular basis of male infertility in the context of evolution.

In support of our approach, evolutionary biologists have observed that male infertility is typically the first barrier to reproductive isolation between two recently diverged species. In cases where the genetic basis of reproductive isolation is understood, the genes share three prominent features; they are rapidly evolving, typically reside on the X chromosome, and are expressed in cells that give rise to sperm. Our lab has identified genomic structures that share these three characteristics, X-amplicons: evolutionarily recent, lineage-specific segmental duplications on the human and mouse X chromosomes that harbor genes expressed almost exclusively during sperm development. Using molecular genetics, development biology, and genomics we are exploring the reproductive functions of X-ampliconic genes, biological significance X-amplicon genomic architecture, and the regulation X-ampliconic gene expression during sperm development. Our long-term goal is to translate our studies of X-amplicons into a better understanding of why 1-2% of otherwise healthy men cannot produce sperm.

Selected Publications:


Gilbert Omenn is a Professor of Internal Medicine, Human Genetics, and Public Health at the University of Michigan. He served as Executive Vice President for Medical Affairs and as Chief Executive Officer of the University of Michigan Health System from 1997 to 2002. He was formerly Dean of the School of Public Health, and Professor of Medicine and Environmental Health, University of Washington, Seattle. His research interests include cancer proteomics, chemoprevention of cancers, public health genetics, science-based risk analysis, and health policy. He was principal investigator of the beta-Carotene and Retinol Efficacy Trial (CARET) of preventive agents against lung cancer and heart disease; director of the Center for Health Promotion in Older Adults; and creator of a university-wide initiative on Public Health Genetics in Ethical, Legal, and Policy Context while at the University of Washington and Fred Hutchinson Cancer Research Center. He served as Associate Director, Office of Science and Technology Policy, and Associate Director, Office of Management and Budget, in the Executive Office of the President in the Carter Administration. He is a longtime director of Amgen Inc. and of Rohm & Haas Company. He is a member of the Council and leader of the Plasma Proteome Project for the international Human Proteome Organization. He is the President of the American Association for the Advancement of Science for 2005-2006.

Omenn is the author of 407 research papers and scientific reviews and author/editor of 17 books. He is a member of the Institute of Medicine of the National Academy of Sciences, the American Academy of Arts and Sciences, the Association of American Physicians, and the American College of Physicians. He chaired the presidential/congressional Commission on Risk Assessment and Risk Management (‘Omenn Commission’), served on the National Commission on the Environment, and chaired the NAS/NRC/IOM Committee on Science, Engineering and Public Policy. He received the John W. Gardner Legacy of Leadership Award from the White House Fellows Association in 2004.

He is active in cultural and educational organizations, and is a musician and tennis player. Omenn received his B.A. from Princeton, the M.D., magna cum laude, from Harvard Medical School, and a Ph.D. in genetics from the University of Washington.

Selected Publications


The Parker laboratory uses an integrative research approach in the general fields of computational biology and functional genomics. The major goal of the lab is to generate mechanistic knowledge about how disease susceptibility is encoded in the non-coding portion of the genome, with a focus on type 2 diabetes. We accomplish this through an interdisciplinary combination of molecular/cellular and computational approaches. Specifically, we generate multiple high-throughput data sets on the genome, epigenome, transcriptome, and proteome across species and in disease-relevant tissues/cells and use computational approaches to integrate and analyze this data. Looking forward, our belief is that these high-throughput biological profiling and analysis approaches will be closely tied to disease diagnosis, prognosis, and treatment—and will therefore have a tremendous influence on medicine.

Selected Publications


We study gene regulation by steroid hormones, focusing on transcriptional mechanisms, hormone-dependent cancers, and sex-dependent gene modulation. Steroid receptors are ligand-activated transcription factors with diverse functions, yet several act via common DNA binding sites and interact with common coregulators. We examine how specific gene control is attained by the androgen receptor (AR).

To study the central role of AR in prostate cancer and to model human disease, we converted the mouse gene to the human sequence (humanized AR mice). Variant hAR alleles in mice confer differences in cancer initiation, progression, and response to therapy. This allows us to study mechanisms of treatment resistance, particularly by somatic AR mutation. In both mouse and human tumors, AR mutants use diverse mechanisms to evade therapy. We are using Next Generation Sequencing to profile differential gene expression and alternative regulatory networks, to improve prognosis and anti-AR treatments.

Sex differences in gene expression occur widely, impacting physiology and incidence of many diseases. We identified via mutant mice a KRAB zinc finger repressor (Regulator-of-sex-limitation) that influences sex-biased expression in liver of genes acting in lipid and steroid metabolism. Rsl deficiency leads to early puberty, lack of dietary stress response and susceptibility to obesity and diabetes. Rsl provides insight into KRAB-ZFP epigenetic mechanisms as well as evolution of this recently expanded gene family.

Selected Publications


Our lab studies mechanisms of DNA repair and with a focus on elucidating how specific defects in repair processes can lead to human disease outcomes, including cancer predisposition, immune system defects and fibrotic disease. We study the genes and pathways that repair DNA double strand breaks and replication associated DNA damage using a combination of molecular, biochemical, cellular and genetic approaches. Projects in the lab include (1) examination of DNA double strand break repair gene mutations associated with human immunodeficiencies and cancer; (2) characterization of the SNM1B DNA nuclease that functions in resolution of replication stress within the Fanconi anemia pathway and (3) molecular characterization of the molecular mechanisms underlying cancer and pulmonary disease in the inherited genome instability disorder, ataxia telangiectasia.

Selected Publications


As the accumulation of knowledge about the agents of life has been increasing exponentially, there are clear signs about us that biologists are becoming aware that we are in great need of efforts to understand living systems more fully. Those on the cutting edge of science are realizing that it may be time to reconsider Schrödinger’s question, What is life? Both reductionism and globalism (i.e., the whole is more than the sum of the parts) are being considered as leading to deeper understandings. In the 21st century integrative biology will become truly integrative as it combines the information about agents gathered by the reductionists in the last half of the 20th century with the global tendencies of complexity research to formulate laws that explain emergent properties characteristic of complex living systems.

Our research team is working to define the role of genetic variation in determining variation in health in the human population at large. Information from population-based samples is being used to address the questions that follow from the reality discussed above. In particular we are asking which variations in which genes, in which environments, influence susceptibility to human disease? Data from the genome level, through intermediate biochemical and physiological levels to the clinically defined endpoint level are available for researching this question.

Selected Publications


Our group focuses on the analysis of high-throughput genetic and sequencing data to understand the genetic basis of cardiovascular and metabolic diseases. We have identified several hundred new genetic regions associated with lipid levels and obesity using whole-genome association studies and are now moving towards fine-mapping these loci to identify functional genetic variants. We are also performing state-of-the-art whole exome and whole genome sequencing studies to identify rare genetic variants with potentially large effects on disease risk. We are currently seeking a postdoctoral fellow with some computational and/or statistical skills and an interest in the biological basis of complex disease, as well as a PhD in a related discipline.

Selected Publications


1) Mechanistic studies of DNA double-strand break repair: DNA double-strand breaks (DSBs) occur frequently and can be lethal if not repaired. Inappropriate repair can lead to chromosomal rearrangements. Understanding the dynamics of these events requires a detailed understanding of the molecular mechanisms of the two main competing DSB repair pathways, nonhomologous end-joining (NHEJ) and homologous recombination (HR). We use genetic approaches to identify novel components of these pathways and characterize their specific mode of action in different repair outcomes. Current focus is on DNA ligase IV, the lynchpin enzyme of NHEJ. This work is performed mainly using yeast.

2) Correlating DNA double-strand break repair to structural genome changes: The reason for exploring DSB repair mechanisms is to understand what happens when they are defective. The global effect of deficient repair on genome stability has historically been difficult to assess. Recent high-throughput genome analysis tools, including microarrays and next-generation sequencing, are therefore being applied to look in an unbiased manner at the correlations between DNA damage, DNA repair, and induced chromosomal aberrations. This work has a strong bioinformatics component, including software development, coupled with human cell and animal wet-lab experimentation.

3) The dynamic process of gene expression: Novel variations on RNA-Seq, especially Bru-Seq, are being used to reveal many new - and often surprising - twists on the dynamic nature of RNA transcript structure and stability in mammalian cells. This returns Dr. Wilson to his early roots from his graduate work on transcription factor biology. Of current interest is the impact of DNA damage on gene expression, independent of changes in genome structure.

4) Correlating transcription to structural genome changes: Most recent endeavors are exploring surprisingly potent connections between the transcriptional landscape, replication, and DSB formation and repair. In brief, high throughput techniques are driving home the understanding that these many nuclear processes must be carefully coordinated in time and space to minimize conflict-driven errors and maintain genome stability.

Selected Publications


