

THE GENOME SCIENTIST

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Genome Sciences Welcomes Five New Faculty Members



Dr. Elhanan Borenstein



Dr. James Bruce



Dr. Su-In Lee



Dr. Judit Villen



Dr. Alejandro Wolf-Yadlin

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Bob Waterston

What a time to be in Genome Sciences! The past two years have been an exciting, yet challenging time.

As you can see from the cover, we have welcomed five outstanding new faculty into the Department – Elhanan Borestein, Jim Bruce, Su-In Lee, Judit Villen, and Alejandro Wolf-Yadlin. They bring real strengths in computational biology and proteomics to what are already strong programs. The diversity of their backgrounds is striking, and they connect us with new areas intellectually, on campus and in the world. You can read more about them on pp. 6-7; suffice it to say here that we are excited by their arrivals and expect great things from them in the coming years.

That we were able to add any new faculty in these tough economic times was itself exciting. In the fall of 2008, just as we were about to launch our search for new faculty, the University announced a hiring freeze, and as the recession took hold in December, the University looked again at exceptions it had granted. Fortunately Genome Sciences was allowed to go ahead, and we were rewarded with wonderful new hires. On the down side, the state has severely cut the University budget with some devastating impacts on some departments. We can only hope that the Governor and Legislature in future budgets recognize the critical role of the University in the future of the state.

On the science front, new technologies, particularly DNA sequencing technologies, are revolutionizing our field, opening whole new avenues of exploration. Fortuitously, the NIH received almost \$10B in ARRA (stimulus) funding in the spring of 2009 just as the new technologies were building up steam. The result has been an explosion in the volume of new genome sequences and in the ways in which DNA sequence can be used to assay biological function. The Department was particularly well positioned to exploit this combination of new technology and an infusion of funds. In conjunction with the award of an NHLBI grant, the Northwest Genomics Center was created and is now in the process of sequencing the protein-coding portions of thousands of patient genomes by September, 2011. With the additional help of the Washington Research Foundation and the Washington's Life Science Discovery Fund, the Department now houses some 16 high throughput DNA sequencing instruments, producing the equivalent of a human genome sequence every hour – simply amazing! But beyond the sheer volume of data, the Department has become a recognized leader in the creative application and analysis of these data sets (see pp. 8-10 for some examples). Not only are we discovering new genes underlying human disease, we are creating the knowledge base that will enable us to understand eventually how yeast, worms, flies and mice work. With all the other wonderful science going on around here, the Department is pulsing with excitement!

Along with our research, education continues to thrive at all levels. Our graduate program is exceptional. Incoming students these past couple years have been simply outstanding; current students are publishing exciting papers; graduating students are securing excellent post-docs. Time to degree is falling. In the undergraduate arena we are revamping our basic genetics course. As part of this we have recruited Michelle Smith to join the faculty as a Lecturer. She comes from a post-doctoral NSF sponsored teaching program at the University of Colorado and will help organize the revised genetics course. Celeste Berg and Bonnie Brewer have also created a "CSI-Seattle" course for a small group of incoming freshmen. In fact, the course staged a "murder" outside the building that the students solved using the latest and greatest DNA forensics. In addition, for the past two summers the Department has hosted a half-dozen or so undergraduates from across the country for a ten-week research experience. The students presented their posters to the Department over pizza and their accomplishments were most impressive. Beyond these more traditional measures, the Department continues to offer its summer public lecture series "Wednesday at the Genome" for the fourth year with 150-200 people attending each of the 4 talks. In addition to all this, as you can read about on p. 12, Maureen Munn's outreach program continues to bring genome science into the high school classroom.

The past couple years have also brought some changes to the administration. In particular, Paula Kassos, who began with me in St. Louis in 1992, retired this past year. She married Dan James and has moved to North Carolina (but she still keeps in touch through email). That left a big hole in the Department, but we were fortunate to have Liz Lancaster as an interim director. In the middle of August, Nancy Cameron came on board as director. Nancy comes to us from the Department of Electrical Engineering and before that she worked in the central administration at the University of Oregon. Nancy brings terrific administrative skills to us and we look forward to working with her in the coming years to make this an ever better department.

This just scratches the surface of activities in Genome Sciences these past couple years. The combination of disciplines, ages and personalities has made Genome Sciences a hive of activity. The faculty continue to receive recognition at all levels (see pp. 4-5). Our impressive faculty interaction map, which depicts the faculty as nodes and their shared projects, grants and papers as edges (courtesy of Bill Noble), grows ever more complex with collaborations bringing people together to solve new problems. The Foegen Building continues to be a joy, with communal areas and the cafeteria facilitating interactions and enough flexible space to allow us to accommodate our new initiatives. Amazingly, in less than five years we have almost filled our half of the building! Please come by for a visit to see first hand the remarkable energy and excitement.

UW LAUNCHES NORTHWEST GENOMICS CENTER

The National Heart, Lung, and Blood Institute (NHLBI) announced Oct. 1, 2009 that the University of Washington (UW) will receive two of the six "Grand Opportunity" NHLBI Large-Scale DNA Sequencing Project awards. The multi-institutional genomics project will examine the genetic connections to heart, lung, and blood diseases that account for three of the leading causes of death in the United States.

The research is co-funded by the National Institutes of Health (NIH) Director's Office. The two-year national project, at a total funding of \$64 million, was made possible by the American Recovery and Reinvestment Act of 2009.

The UW will receive \$25 million to launch the Northwest Genomics Center, one of two sequencing centers for the project. The second sequencing center will be located at the Broad Institute of MIT and Harvard in Cambridge, Mass.

The UW will also receive a \$5.2 million grant, under the direction of Dr. Michael Bamshad, UW professor of pediatrics in the Division of Genetic Medicine, to manage the lung disease population research portion of the national project. Ohio State University, Washington University in St. Louis, and the University of Virginia are the other participating institutions managing cardiovascular and blood disease projects.

"This extraordinary collaboration promises to deepen our understanding of the complex interactions of genetics, the

environment, and lifestyle choices, helping us bring the best science to the patients who need it most," said NHLBI Director Dr. Elizabeth G. Nabel.

The Northwest Genomics Center in Seattle will be among the first new, large-scale genomics centers focused entirely on medical sequencing to be created in the United States in more than a decade. The UW also received \$2 million in funding from the state's Life Sciences Discovery fund to support the Center's infrastructure.

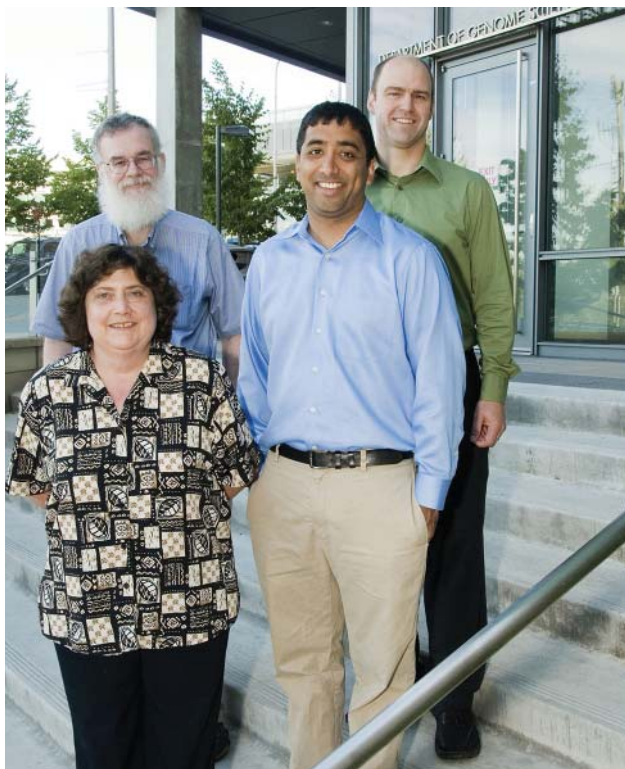
"The Northwest Genomics Center will apply cutting edge, next generation sequencing technology to uncover the differences in our genetic code and explore how these may influence traits, such as cholesterol and blood pressure, that impact our risk for developing cardiovascular disease," said Dr. Debbie Nickerson, UW professor of genome sciences and one of the principal investigators for the new Center. Other principal investigators are Drs. Jay Shendure, Philip Green, and Mark Rieder, who are also faculty members in the UW Department of Genome Sciences.

"This is an extraordinary team effort to which we all bring individual expertise," Nickerson said. She and Rieder are leaders in medical sequencing of cardiovascular, blood and lung diseases. Shendure is one of the pioneers in the development and application of next generation sequencing technology, and Green is a world leader in developing new software tools for sequence analysis, including the tools that helped to generate the human genome sequence.

Bamshad, who will head the lung disease component of the national project, is noted for his work on common genetic variations in the United States population and how these affect individual and ethnic group differences in susceptibility to disease. The NHLBI Large-Scale DNA Sequencing Project will explore many common forms of heart, lung, and blood diseases. The ethnically diverse individuals to be studied from the large, long-term population studies have given their permission for the information from their DNA to be shared with other investigators.

"The national project will tackle not only susceptibility to these common, complex diseases, but also resistance," Nickerson said. She noted that it is possible that understanding disease resistance could provide new avenues for the prevention and treatment of these disorders. For example, some of the research groups will compare samples from people who have very high cholesterol against those who have very low cholesterol to see what genes and differences contribute to these extremes.

"Cardiovascular disease is a complex, common disorder that affects millions of people and leads to early death in adults from heart attacks and strokes," said Nickerson. Chronic lung



Drs. Debbie Nickerson, Phil Green, Jay Shendure, Mark Rieder

UW Launches Northwest Genomics Center, continued

diseases affect more than 35 million Americans. One out of every 7 deaths is from lung disease, making it the third leading cause of death.

“Unlike rare diseases, which usually follow a simple pattern of inheritance of variation in one gene,”she explained,“it has been very difficult to sort out the complicated genetics of the multiple factors that contribute to heart disease and to lung disease, and how they interact with environmental influences, such as smoking or nutrition. For example, heart disease runs in some families, but the inheritance doesn’t follow simple rules.”

In the lung disease section of the NHLBI Large-Scale DNA Sequencing Project, Bamshad will lead an effort to identify rare and common gene variations that influence the severity of lung diseases such as asthma, chronic obstructive pulmonary disease, acute lung injury, pulmonary hypertension, and cystic fibrosis.

“Our goal is to better understand the biology of lung diseases, improve their diagnosis and treatment, and gather information that may lead to novel therapeutics,”Bamshad noted. “We want to make strides in the management of a group of diseases that impact the youngest and the oldest in our country.”

Grand Opportunities, or GO, is an ARRA program which supports high-impact ideas that may lead to new fields of investigation and that may accelerate critical breakthroughs.

“This is one of those times in science when it is just the right moment to scale newly emerging technologies to obtain important medical insights,”Nickerson said. “Over the past two years genome technology has improved vastly in terms of lower costs and faster methods that have increased research productivity. It’s the right time for genome sciences to begin to have an impact on medicine.”

The UW has been among the world’s leaders in developing and testing new technologies and analytical approaches for genomics. These advances have prepared UW scientists to take on the challenge of large population studies to uncover the genetics of cardiovascular and lung diseases. This new genome science effort also builds on a 60-year history of UW research on the heritability of lipid disorders leading to premature heart attacks and on the medical genetics of other common, chronic diseases.

A few of the many UW advances in genome research that will be applied at the Northwest Genomics Center include:

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BREWER ELECTED TO AAAS



Dr. Bonny Brewer has been elected a fellow of the American Association for the Advancement of Science. The AAAS, publisher of the journal *Science*, is an international non-profit organization dedicated to advancing science around the world.

Dr. Brewer’s research focuses on yeast chromosomes and their origins of replication - the sites in DNA where replication begins.

DUNHAM NAMED ALLEN SCHOLAR



Dr. Maitreya Dunham has been named a Rita Allen Foundation Scholar. The Rita Allen Foundation supports outstanding scientists in the early stages of their research careers in the fields of cancer, neuroscience and immunology, and other educational programs. Dr. Dunham also received the 2009 Marian E. Smith Junior

Faculty Research Award from the UW School of Medicine.

Dr. Dunham combines experimental evolution with genomic analysis to study the structure and function of genetic networks in yeast.

HALL, GOTTSCHLING ELECTED TO AMERICAN ACADEMY OF ARTS & SCIENCES

Dr. Benjamin Hall, Professor Emeritus of Genome Sciences and of Biology, and Dr. Daniel Gottschling, Member, Fred Hutchinson Cancer Research Center and Affiliate Professor of Genome Sciences, have been elected to the American Academy of Arts & Sciences, one of the nation’s oldest and most prestigious honorary societies.



Dr. Hall, a past Chair of the former Department of Genetics, is known for his studies in yeast transcription. These studies led to two important inventions enabling the use of yeast cells for genetically engineered production of biopharmaceuticals, including hepatitis B vaccine, human insulin, and human serum albumin.



Dr. Gottschling is currently interested in understanding the striking link between increasing age and the incidence of cancer in humans.

FELSENSTEIN RECEIVES JOHN J. CARTY AWARD



Dr. Joseph Felsenstein, Professor of Genome Sciences and of Biology, has received the 2009 John J. Carty Award for the Advancement of Science from the National Academy of Sciences. Dr. Felsenstein's research has revolutionized population genetics, phylogenetic biology, and systematics by developing a sophisticated computational framework to deduce evolutionary relationships of genes and species from molecular data.

Dr. Felsenstein has also recently received the American Institute of Biological Sciences Distinguished Scientist Award.

MACCOSS, MALIK RECEIVE PECASE

Dr. Michael MacCoss, Associate Professor of Genome Sciences, and Dr. Harmit Malik, Associate Member, Fred Hutchinson Cancer Research Center and Affiliate Associate Professor of Genome Sciences, have been awarded the nation's highest honor for scientists at the outset of their professional careers, the Presidential Early Career Award for Scientists and Engineers. Dr. Malik has also recently received the 2010 Vilcek Prize for creative promise in biomedical science.



Dr. MacCoss' research focus is in the development of stable isotope and mass spectrometry based approaches to improve our understanding of biology on a molecular, cellular, and whole organism level.



Dr. Malik is interested in evolutionary studies of genetic conflict to gain insight into their mechanisms and consequences.

HORWITZ NAMED MSTP DIRECTOR



Dr. Marshall Horwitz, Professor of Pathology and of Medicine, Adjunct Professor of Genome Sciences, has been named Director of the University of Washington's Medical Scientist Training Program.

The UW MSTP is one of the country's leading physician-scientist training programs.

Dr. Horwitz's research interests are focused on cancers of the blood and bone marrow failure syndromes.

KING AWARDED DAWSON PRIZE



Dr. Mary-Claire King has been awarded the 2010 Trinity College Dublin Dawson Prize in Genetics. This award is given every two years to a geneticist of international prominence

Dr. King is the American Cancer Society Research Professor in the departments of Medicine and Genome Sciences. Her research interests include breast and ovarian cancer, inherited deafness, and systemic lupus erythematosus.

MOTULSKY RECEIVES MCKUSICK & LIFETIME ACHIEVEMENT AWARDS



Dr. Arno Motulsky, Professor Emeritus of Medicine and of Genome Sciences, has received the inaugural Victor McKusick Leadership Award from the American Society of Human Genetics, in recognition of his pioneering work in medical genetics. Dr. Motulsky was also recently awarded the Lifetime Achievement Award from

the American College of Medical Genetics, the foundation's highest honor, and the 2009 Bernard Heller prize from Hebrew Union College.

Dr. Motulsky is known among scientists as the "father of pharmacogenetics," a field that explores the role of genetic variation in response to drugs.

SHENDURE RECEIVES PROSTATE CANCER FOUNDATION AWARD



Dr. Jay Shendure, Assistant Professor of Genome Sciences, has received a 2010 Prostate Cancer Foundation Young Investigator award. The award provides innovative scientists with three years of funding to pursue transformational research questions that may help men affected by prostate cancer. Dr. Shendure and his re-

search group are working to eliminate technological obstacles to understanding the genetic events that cause the start and spread of prostate cancer.

WATERSTON HONORED



Dr. Robert Waterston, Professor and Chair of Genome Sciences, was recently awarded an honorary doctorate from Washington University in St. Louis. Dr. Waterston is known for his pioneering contributions to the field of genomics, including his leading role in the Human Genome Project.

ELHANAN BORENSTEIN, ASSISTANT PROFESSOR



Elhanan Borenstein, Ph.D., comes to Genome Sciences from Stanford University and The Santa Fe Institute, where he held a joint postdoctoral position. He is broadly interested in evolutionary systems biology – an emerging field that examines the interplay between the evolutionary process and the organization of complex biological systems. His research in this field is multidisciplinary by nature and spans several levels of abstraction, ranging from computational analysis of complex networks and high-throughput data to theoretical studies of mathematical and computational models. Most recently, he has been focusing on developing a computational framework for uncovering fundamental design principles and assembly rules of metabolic networks, characterizing the dynamics that govern their evolution, and identifying topological signatures of adaptation. Applying this framework to metagenomic data to study functional dependencies and ecological interactions in microbial communities, especially those that inhibit the human body, is one of the exciting challenges his lab will be addressing. Additional research interests include the origins of modularity, robustness and plasticity, complex systems (with an emphasis on complex biological networks), genotype-phenotype maps, the evolution of learning and culture, population genetics and evolutionary theory.

Dr. Borenstein comments that “the Department of Genome Sciences is a true powerhouse of genomic research and is home to a brilliant and exceptional group of scientists. I am especially excited about the unique and vibrant interface between computational and experimental biologists in the department and about its collaborative and collegial nature. I am thrilled to join this community and to work closely with faculty and students.”

Elhanan has moved to Seattle with his wife, fashion designer and business executive, DT Levy.

SU-IN LEE, ASSISTANT PROFESSOR



Su-In Lee, Ph.D., came to Genome Sciences from Stanford University where she completed her Ph.D. under the supervision of Dr. Daphne Koller. Her research focuses on the development of machine learning techniques for understanding the genetic basis of complex traits. Humans differ in many ‘phenotypes’, ranging from appearance to disease susceptibility, and many of them are largely determined by each individual’s specific ‘genotype’. In recent years, it has become possible to retrieve an individual’s sequence information on a genome-wide scale, as well as high-throughput functional information such as RNA/protein expression levels. The complexity of cellular mechanisms induced by sequence variations, however, still makes it difficult to infer the causal relationships between genotype and phenotype and the underlying molecular-level mechanisms. The key to success lies in combining theoretically founded computational frameworks with a comprehensive understanding of biological systems. Her goal is to address the challenge by developing effective machine learning algorithms that can translate sophisticated biological processes into robust statistical models; can infer their underlying mechanisms from high-dimensional, sparsely sampled data; can combine information from multiple sources of genomic data; and can learn such models from data efficiently.

Dr. Lee comments “my research area is at the junction of multiple disciplines -- computer science, medical science and biology. I believe that to succeed in this field, it is important to be in an institution that is strong in the individual fields and that has active collaborative efforts between the disciplines. In that sense, The University of Washington (UW) provides rare opportunities to develop my research. UW is one of very few universities that are strong in all fields relevant to my research: computer science, genetics and medical research. Especially, the Department of Genome Sciences, with strong faculty members with diverse research interests involving genetics, proteomics and computational biology, is an ideal department for me to conduct my research.”

JAMES BRUCE, PROFESSOR

James E. Bruce, Ph.D., came to Genome Sciences from Washington State University where he was Professor of Chemistry and Director of Proteomics and Biological Mass Spectrometry. "The opportunity to join Genome Sciences allowed us to take our research to new levels. This department is an exceptionally exciting place to be since the research done here has shaped much of what is today's large-scale biology and genomics research. I feel very fortunate to be a part of this environment and especially, to be a part of Genome Sciences growth in the area of proteomics."

Dr. Bruce's research interests include technology development and application to the study of the proteome for improved comprehension of functional pathways in healthy cells, disease and the biology of microbial systems. This broadly encompasses areas from fundamental research on ion physics that will enable advanced measurements of the proteome, to the development and application chemical biology and informatics methods that can yield new insight on the proteome relevant to signal transduction, drug resistance and cancer, and many other areas.

"The ability to detect and identify protein interactions in native biological systems in an unbiased way will have a significant impact on assignment of function to genes and our ability to visualize functional interaction networks and topologies in live cells."

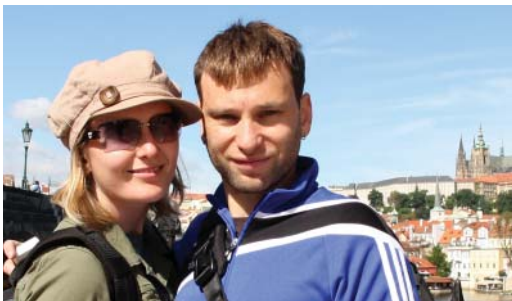
Jim and his wife Xiaoting Tang, a proteomics research scientist with a local pharmaceutical company, moved to Seattle in December of 2008. Their son, Anthony James Bruce, was born on March 12, 2009.

JUDIT VILLEN, ASSISTANT PROFESSOR

Judit Villen, Ph.D., came to Genome Sciences from Harvard University where she had been a postdoctoral fellow in the lab of Dr. Steve Gygi. Dr. Villen comments that "Genome sciences felt like the best place for developing my research program: it is a very technology-driven department, and it is a place where it will be easy to integrate genomics and proteomics approaches towards the understanding of regulation at multiple levels."

The Villen Lab seeks to develop and apply novel technologies for proteome characterization to answer fundamental questions in cell biology and disease, using quantitative mass spectrometry to measure dynamic changes in protein abundances, protein post-translational modification states, and to characterize interaction partners across multiple cellular states.

They are particularly interested in studying protein phosphorylation as a general regulatory mechanism in the cell involved in a myriad of functions: how phosphorylation is integrated into the multiple responses to shape the proteome, and how signaling circuits evolved to accommodate proteome functional complexity.

ALEJANDRO WOLF-YADLIN, ASSISTANT PROFESSOR

Alejandro Wolf-Yadlin, Ph.D., comes to Genome Sciences from Harvard University, where he held a postdoctoral position in the MacBeath Lab. He is interested in understanding receptor tyrosine kinase initiated cellular signaling networks and developing new high-throughput techniques to study cellular signaling in general. In particular the Wolf-Yadlin Lab will focus on the application of mass spectrometry, lysate arrays, qtPCR and phenotype based assays to study cellular signaling and its relationship to gene expression and cell state. Their goal is to understand the difference in the dynamics and topology between cellular signaling networks of different disease states and healthy cells, hoping this will allow insight on how the cell functions and which proteins or genes might represent good drug targets for therapeutic applications.

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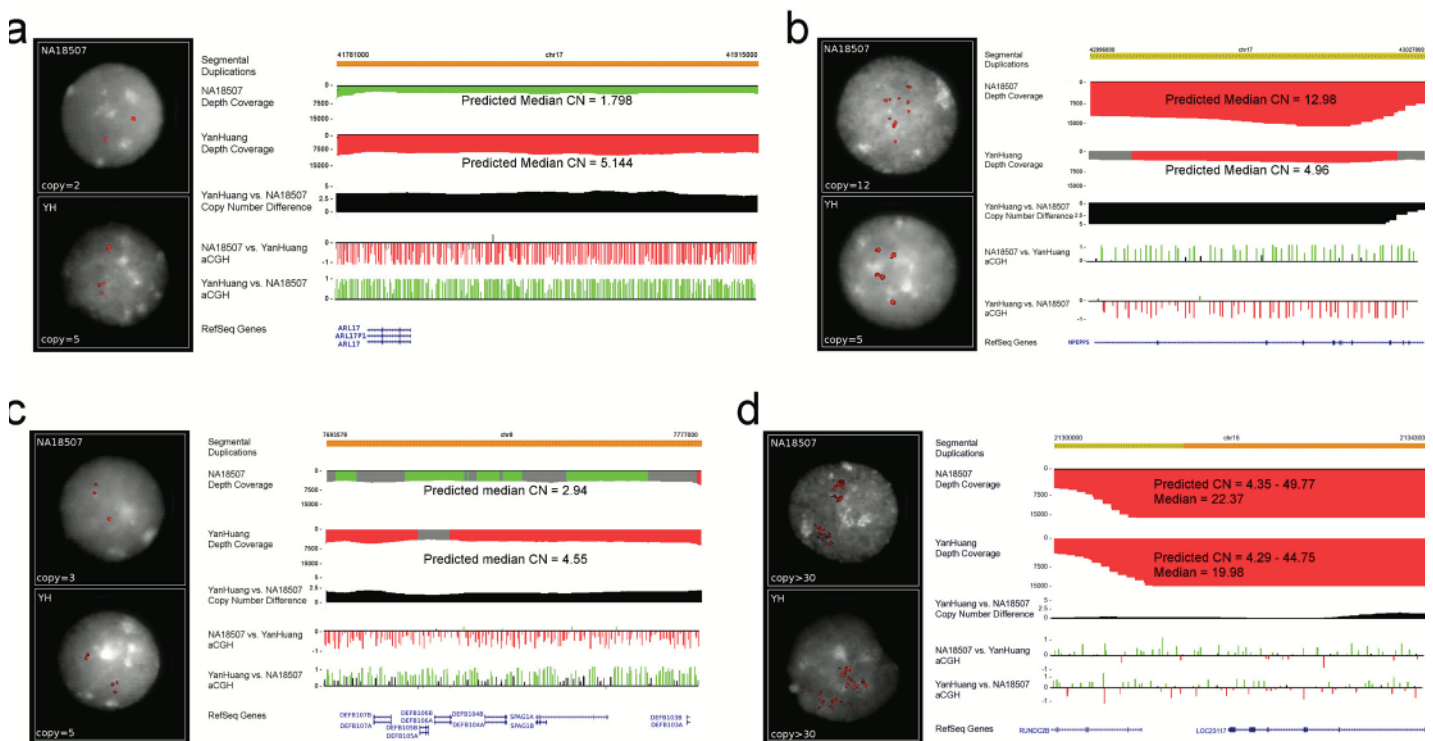
SEGMENTAL DUPLICATIONS: FROM EVOLUTION TO HUMAN COPY-NUMBER VARIATION

The architecture of any genome is constantly being reorganized through addition and deletion of DNA segments. Segmental duplications are fragments of DNA, usually larger than 1 kb with at least 90% sequence identity, that have been associated with susceptibility and resistance to disease in humans (such as lupus, Crohn's disease, mental retardation, schizophrenia, color blindness, psoriasis, and age-related macular degeneration). Segmental duplications often contain genes, many of which have an unknown function. The spotted distribution of duplications in the human genome is also responsible for a genomic flexibility that might have resulted in some evolutionary adaptations giving rise to some uniquely human characteristics.

The Eichler lab aims to understand such human variation and their impacts in terms of evolution and relation to disease. In one of our recent studies, we aimed to answer a fairly important question: When did these duplications emerge? To address this question, we focused on the genomes of three closely related primate species: macaques, orangutans and chimpanzees. All are descended from a single ancestral species that lived about 25 million years ago and by comparing the DNA sequences of the humans to the other species, we were able to identify duplications that are species specific (belonging only to the lineages leading to these species) from other duplications that were shared by their common ancestors.

The main finding was that there is an excess of duplications that are shared by human and chimpanzees, indicative of a higher rate of duplications in the time of the ancestral species leading to chimps and humans. This is striking because this happened in a period of time in which other mutational processes, such as changes in single basepair changes were slowing down. These duplications might have sensitized our genome by creating regions that are especially prone to large-scale reorganizations and their negative effects on the genome. However, these regions also exhibit signs of being under positive selection, meaning that some of the duplications could have conferred advantages on the individuals who inherited them, suggesting that the negative selection on these duplications could have been outweighed by the selective advantage of having these newly minted genes.

However, not all these duplications are fixed in the human population. Every individual might have a different number of copies of each duplication resulting in different susceptibilities to different diseases. Determining the copy-number, content, and loca-



Predicted copy-numbers from WGS data along with arrayCGH and FISH validation. a) 17q21.31 locus, b) the NPEPPS gene. c) the defensin gene family cluster of 8p23.1. d) Due to the known mosaic architecture for this high copy locus (>30 copies), both arrayCGH and FISH methods fail to accurately estimate copy-number difference between NA18507 and YH genomes: despite the fact that sequence depth predicts ~2 more copies in NA18507.

Segmental Duplications: From Evolution to Human Copy-Number Variation, continued

tion of segmental duplications is an important step in understanding the health significance of gene copy-number variation. In fact, to count whether a person has one, two, three or more copies of a gene is surprisingly difficult. By using different methods such as array comparative genomic hybridization (arrayCGH) scientists have been able to analyze the entire genome of a person and say that an individual has more or fewer copies of a particular gene with respect to a reference individual, but could not predict the absolute number of copies.

Here in the Eichler lab, we developed a newly designed computational method that has been proven useful in counting copies of duplicated genome sequences and in doing initial assessments of their contents. We have named our method mrFAST, an acronym for micro-read Fast Alignment Search Tool and it is likely to be one of the first personalized genomic approaches to characterize personal susceptibilities to disease. Next-generation technology for sequencing the human genome has far greater detection power and costs substantially less than the traditional sequencing and may lead to a fuller understanding of the patterns and significance of human genetic variation.

We have further examined the much-studied genomes from three healthy individuals: a European (DNA research pioneer James D. Watson), a Yoruba African individual from Nigeria, and a Han Chinese. We were able to predict copy-number differences among the individuals, even when there were many copies, such as 5 in one person compared to 12 in another. Several of the validated gene differences are known to be of biomedical relevance. They include, for example, genes related to eye and skin diseases, and many others that play a role in autoimmunity. We have also noted that several human genes with the most variable copy numbers correspond to the burst of segmental duplications that occurred within the common ancestor of apes and humans, pinpointing regions of the genome with an unusual higher mutation rate and showing, one more time, that evolution and disease are two tightly correlated processes, both mutually informing one another.

INTERNATIONAL NETWORK TO COMBAT MALARIA DRUG RESISTANCE

The WorldWide Antimalarial Resistance Network (WWARN), a new international collaborative of malaria scientists, was launched June 12, 2009 with a \$20 million grant from the Bill & Melinda Gates Foundation. The scientific director of the network is Carol Sibley, UW professor of genome sciences.

WWARN maps the emergence of resistance to antimalarial drugs and guides global efforts to control and eradicate the disease. The network will provide the comprehensive and rigorous evidence needed for policy makers to select the most effective anti-malarial treatments and to formulate strategies to control resistance wherever it arises.

Malaria is preventable and treatable, yet one million people die from malaria each year, most of them children. About 2.5 billion people, or 40 percent of the world's population, are at risk of the disease. These people live mainly in the poorest countries of the world, those least able to provide effective controls against the disease.

Prevention of infection is one important facet of malaria control, but with no vaccine against malaria, treatment relies on antimalarial drugs. The World Health Organization (WHO) has declared that the emergence of resistance to these drugs could seriously undermine efforts to control the disease.

WWARN will integrate the efforts of researchers, NGOs and public health experts in malaria-endemic areas around the world. Four years in planning, the initiative was born in the scientific community as malaria scientists became aware that broad collaboration was essential to achieving the long-term goal of eliminating the disease. The international collaborative effort will be administered and supported from Oxford University under the directorship of Philippe Guerin at the Centre for Tropical Medicine. WWARN will work in close collaboration with WHO to enhance antimalarial resistance surveillance.

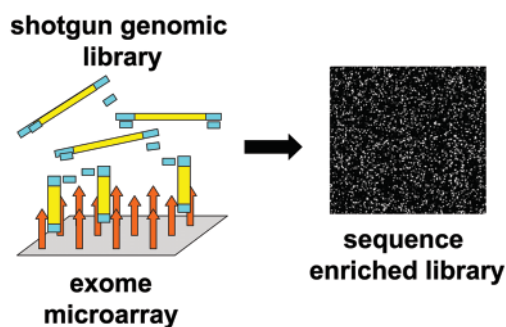
The collaboration will provide a platform for all malaria scientists to share results, thereby improving the coverage, quality, and timeliness of the available data. This will give an up-to-the-minute picture of the effectiveness of antimalarial drugs at national, regional and global levels, and enable policy makers to respond more quickly to early signs of resistance.

"Everyone involved in the war against malaria understands that this is critical," Sibley said. "We need to gather the very best intelligence to alert the malaria community to signs of resistance and mobilize our best weapons on the frontline."

NEXT GENERATION MENDELIAN GENETICS

The Bamshad, Nickerson, and Shendure Labs have sought to develop methods for targeted sequencing of all protein-coding regions ('exomes') in the human genome, to reduce costs while enriching for discovery of highly penetrant variants. We recently reported on the targeted capture and massively parallel sequencing of the exomes of 12 humans (Ng et al., *Nature*, 2009). These included eight HapMap individuals representing three populations, and four unrelated individuals with a rare dominantly inherited disorder, Freeman–Sheldon syndrome (FSS).

Exome capture by array hybridization



We demonstrated the sensitive and specific identification of rare and common variants in over 300 megabases of coding sequence. Using FSS as a proof-of-concept, we showed that candidate genes for Mendelian disorders can be identified by exome sequencing of a small number of unrelated, affected individuals. Application of this strategy to an unsolved Mendelian disorder identified recessive mutations in *DHODH* as the cause of Miller syndrome, the first genetic disease solved by exome sequencing (Ng et al., *Nature Genetics*, 2010). We are currently extending this strategy to additional Mendelian disorders as well as to common diseases with more complex genetics.

Targeted capture and massively parallel sequencing of 12 human exomes. Ng SB, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, Bamshad M, Nickerson DA, Shendure J. *Nature*. (2009) **461**: 272-6.

Exome sequencing identifies the cause of a mendelian disorder. Ng SB, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, Shendure J, Bamshad MJ. *Nat Genet*. (2010) **42**: 30-5.

UW Launches Northwest Genomics Center, continued

- Methods to isolate the protein-coding regions of the human genome known as the exome, a development that contributes to the ability to analyze thousands of human genomes (Jay Shendure)
- Studies of how differences in single nucleotides in human DNA can underlie certain forms of genetic diseases and responses to medications (Debbie Nickerson and Mark Rieder)
- The creation of computer programs that reduce the noise in and improve the reliability of sequence data (Philip Green)

Several other recently funded economic stimulus research projects, such as studies of the genetics of neuropsychiatric disorders, including autism and schizophrenia, will also benefit from the expertise and powerful next generation technology of the Northwest Genomics Center.

Nickerson said that the scale-up of next generation sequencing is poised to “change medicine in ways we cannot predict. The American Recovery and Reinvestment Act of 2009 is medicine’s moon shot, and we are looking forward to participating in this exciting new effort.” (*article courtesy of Leila Gray, UW News*)

Dr. Alejandro Wolf-Yadlin, continued

Dr. Wolf-Yadlin comments “after my interview job at UW I knew it would be very hard to say no to an offer from Genome Sciences. There are many faculty members and scientists in the departments with whom I have overlapping research interest and many more with whom I would like to work. The high quality of the students and the sheer number of great research projects ongoing within the department not to mention the university was enough reason for me to want to come to GS. If we add to that the collegial atmosphere in the department, which encourages collaboration and interaction among faculty members and students, it was an easy choice.”

Alejandro recently married, and his wife, Dina Fomina Yadlin is currently finishing her doctoral thesis in Molecular and Cellular Biology at Harvard. He is originally from Chile and when not in the lab can usually be found at the nearest soccer field.

CONGRATULATIONS TO RECENT GRADUATES!

Shameek Biswas (Ph.D. in Genome Sciences)
"Statistical Methods for Analyzing and Interpreting High-Dimensional Phenotypes"

Cindy Desmarais (Ph.D. in Genome Sciences)
"Exploring Patterns of Polymorphism and Divergence in the Human Genome"

Diane Dickel (Ph.D. in Genome Sciences)
"Genomic Analysis of Transcribed Microsatellite Repeats in Psychiatric Disease and Primate Evolution"

Lazar Dimitrov (Ph.D. in Genome Sciences)
"Genetic Analysis of Mitochondrial Genome Instability in *S. cerevisiae*"

Mark Enstrom (Ph.D. in Genome Sciences)
"A Genome Scale Phenotype Screen to Determine Carbon Source Utilization and Stress Tolerance Pathways in *Francisella novicida*"

Geoff Findlay (Ph.D. in Genome Sciences)
"*Drosophila* Seminal Fluid Proteins: Proteomic Identification and Evolutionary Analysis"

Jeff Kidd (Ph.D. in Genome Sciences)
"Mapping and Sequencing Human Genomic Structural Variation"

Michael Hoopmann (Ph.D. in Genome Sciences)
"Improving the Aim of Shotgun Proteomics: Software and Technology for High-resolution Mass Spectrometry"

Zhaoshi Jiang (Ph.D. in Genome Sciences)
"An Evolutionary Reconstruction of Human Segmental Duplications"

Chul Joo Kang (Ph.D. in Genetics)
"The Full Likelihood Approach for Variation of Recombination Rate Using Markov Chain Monte Carlo Method with a Hidden Markov Model"

Kristen Lewis (Ph.D. in Genome Sciences)
"Genomic Approaches to Forensic DNA Analysis"

Graham McVicker (Ph.D. in Genome Sciences)
"The Roles of Natural Selection and Germline Gene Expression in Primate Genome Evolution"

Brig Mecham (Ph.D. in Genome Sciences)
"Supervised Normalization of Microarrays"

Angela Poole (Ph.D. in Genome Sciences)
"The Mechanisms Underlying Mitochondrial Dysfunction in Parkinson's Disease"

Rori Rohlfs (Ph.D. in Genome Sciences)
"The Role of Null Distributions in Statistical Genetics"

Steve Salipante (Ph.D. in Genome Sciences)
"A Genomic Approach to Fate Mapping: or, How I Learned to Stop Worrying and Love Somatic Mutation"

Will Sheffler (Ph.D. in Genome Sciences)
"A Volumetric Energy Function For Protein Core Packing"

Troy Zerr (Ph.D. in Genome Sciences)
"Genotyping Human Genomic Structural Variation"

2009 INCOMING CLASS

Anna Brosius, Williams College, UW MSTP
Caitlin Connelly, University of Washington
Rachel Diederich, University of Chicago
Adam Gordon, University of Chicago
Sharon Greenblum, Northwestern University
Joe Hiatt, Stanford University, UW MSTP
Blake Hovde, Pacific Lutheran University
Tzitziki Lemus Vergara, National Autonomous University of Mexico
Aaron Miller, University of California, Santa Cruz
Alessandra Oddone, Wellesley College
Rose Okamoto, University of Washington
Andrew Stergachis, University of Chicago, UW MSTP
Jeff Vierstra, University of Wisconsin
Chad Weisbrod, Washington State University

2010 INCOMING CLASS

Joshua Burton - Princeton University
William Edelman - University of New Mexico
Keolu Fox - University of Maryland
Tanya Grancharova - Loyola University of Chicago
Nik Krumm - Johns Hopkins University, UW MSTP
Akash Kumar - University of Minnesota, UW MSTP
Jennifer McCreight - Purdue University
Alexander Nuttle - Duke University
Max Press - Reed College
Matt Rich - Princeton University
Jeff Staples - Brigham Young University
Benjamin Vernot - Carnegie-Mellon University
Jennifer Wagner - University of Wisconsin

RECENT STUDENT FUNDING AWARDS

Joe Hiatt - NRSA individual fellowship
Jacob Kitzman - NSF fellowship
Ray Malfavon-Borja - NRSA individual fellowship

GENOME SCIENCES EDUCATION OUTREACH: INVOLVING STUDENTS IN AUTHENTIC RESEARCH

In answer to the proverbial question, “What did you do at school today?” students throughout the Pacific Northwest might answer, “I carried out research on smoking behavior.” These students and their teachers are part of an innovative program developed by Genome Sciences Education Outreach (GSEO) that involves classrooms in conducting an authentic epidemiological study of genetic and environmental factors associated with becoming a highly addicted smoker.

With funding from the National Institute on Drug Abuse, GSEO has developed a program called StarNet: Investigating the Effects of Genes and Environment on Smoking Behavior. This multi-year project involved over 4000 high school and college students in designing and implementing a research investigation that compares smoking behavior, environmental factors, and some genetic factors among hundreds of adult smokers and nonsmokers. Program staff Maureen Munn and Megan Brown, with guidance from the PI, Debbie Nickerson, and coPI, Gail Jarvik, have worked with teachers, scientists, and bioethicists to develop the curriculum and smoking behavior research study. The UW Center for Clinical Genomics coordinated aspects of the smoking study, including recruiting and meeting research subjects and purifying DNA from subjects’ blood. The UW Clinical Research Center, a resource of the Institute of Translational Sciences, provided the facilities to meet subjects and take the blood draw.

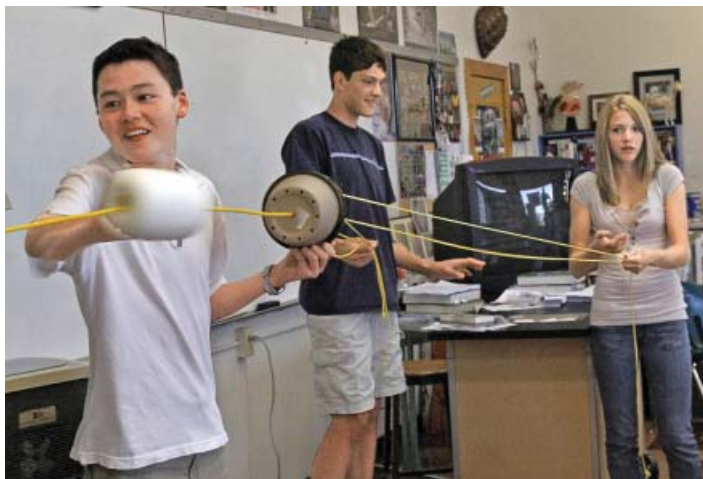
Over the past three years, students contributed to several aspects of the research study. Early in the program, students wrote questions for the research questionnaire, which collects information about subjects’ environment and smoking behavior. Later, students genotyped subjects’ DNA at several candidate genes that may be associated with susceptibility to nicotine addiction. Data from the study have recently been entered into a user-friendly database, and in the coming years, students will use this “Smoking Behavior Database” to answer their own research questions about factors that may influence smoking behavior. Addressing the benefits of this program, one teacher stated:

“...this is giving students the idea that science and scientists don’t know everything. Right now we are actually using a database to draw conclusions on things that aren’t even published or known. They might be the first one to make the comparison and to write a conclusion, which I think is a very cool cutting edge type of activity for students to do.”

With the change in focus of the student research experience from a wetlab (genotyping) to an online “e-science” experience (analysis of data in the database), we can now ask several significant educational research questions: Is the e-science research experience effective in teaching students about the nature and process of science, genetics, neuroscience, and bioethics? What elements of a technology-delivered curriculum are needed so students can formulate testable research questions and develop rigorous scientific arguments using the database? Will students and their teachers view e-science as real science? GSEO, in collaboration with the UW College of Education, will explore these and other questions as part of a new project funded by the National Science Foundation called Exploring Databases: STEM* learning and authentic research in the high school classroom.

Exploring Databases is the latest in a series of genetics-focused education programs for K-12 teachers and students that GSEO has created and implemented over the last 16 years. These programs provide interdisciplinary, hands-on science curricula, teacher professional development, and equipment, to support accurate teaching of genetics, genomics and bioethics in K-12 classrooms. Critical to the success of these programs have been the contributions of scientists, ethicists, teachers and other science educators, who have shared their expertise during curriculum development, made presentations in teacher workshops, or

assisted in classrooms during hands-on experiments. Information about current and past projects and associated instructional materials are available at <http://chroma.gs.washington.edu/outreach>.



Students in a Billings, Montana high school use a model neuron to learn how neurons communicate with each other as part of the Investigating Smoking Behavior curriculum. The rope neuron model was designed by Eric Chudler, UW Department of Bioengineering, and is described at <http://faculty.washington.edu/chudler/chmodel.html>.

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