The Genetic Basis Of Human Cancer

Books such as Richard Dawkins's The Selfish Gene have aroused fierce controversy by arguing for the powerful influence of genes on human behavior. But are we entirely at the mercy of our chromosomes? In Are We Hardwired?, scientists William R. Clark and Michael Grunstein say the answer is both yes--and no. The power and fascination of Are We Hardwired? lie in their explanation of that deceptively simple answer. Using eye-opening examples of genetically identical twins who, though raised in different families, have had remarkably parallel lives, the authors show that indeed roughly half of human behavior can be accounted for by DNA. But the picture is quite complicated. Clark and Grunstein take us on a tour of modern genetics and behavioral science, revealing that few elements of behavior depend upon a single gene; complexes of genes, often across chromosomes, drive most of our heredity-based actions. To illustrate this point, they examine the genetic basis, and quirks, of individual behavioral traits--including aggression, sexuality, mental function, eating disorders, alcoholism, and drug abuse. They show that genes and environment are not opposing forces; heredity shapes how we interpret our surroundings, which in turn changes the very structure of our brain. Clearly we are not simply puppets of either influence. Perhaps most interesting, the book suggests that the source of our ability to choose, to act unexpectedly, may lie in the chaos principle: the most minute differences during activation of a single neuron may lead to utterly unpredictable actions. This masterful account of the nature-nurture controversy--at once provocative and informative--answers some of our oldest questions in unexpected new ways

Genetics of Fitness and Physical Performance is the first comprehensive reference on the role of the genes in influencing individual variation in fitness and performance. This essential compendium reviews the past 25 years of accumulated evidence on the genetic basis of health- and performance-related fitness phenotypes. Focusing on the interests of sport scientists, the authors provide insight into the significance of this research on nearly every aspect of the study of human physical activity. The book presents the biological basis of heredity and explains the concepts and methods of genetic epidemiology and molecular biology that are necessary to understand this specialized field. With the rapid advances in molecular biology and the paradigms of human genetics, exercise scientists face a dynamic and vibrant new field. This book offers readers new opportunities to better understand atherosclerosis, noninsulin dependent diabetes, obesity, and hypertension by searching for single gene effects and identifying susceptibility genes. The authors review the evidence on the role of the genes for human traits as it pertains to the exercise science field. And they explore the scientific, practical, and ethical issues that confront exercise scientists as progress is made in this field. Genetics of Fitness and Physical Performance is vital reading for scholars in the field of exercise and sport science to understand how recent discoveries in genetics might shape their future research.

Every year there are new and exciting developments in assisted human reproduction, but how much do we really know about the underlying causes of infertility? This volume explores recent progress in the understanding of the genetics of spermatogenesis and male infertility. Topics include fundamental advances and current problems in the development and function of the testis, an outline of clinical findings in male infertility and an overview of the role of the Y chromosome in male fertility. Comprehensive critiques of posttranscriptional control during spermatogenesis, mammalian meiotic sterility, and comparative genetics of human spermatogenesis from the perspective of yeast, Drosophila and mice provide a global overview of the field.

Genome-wide Genetic Basis of Human Hepatitis B Virus

By the Origin of Human Inequalities : Sequel to Chas : Darwin Origin of Species

Methods for the Analysis of Human Genetic Variation in the Search for the Genetic Basis of Human Disease

How the Human Genome Works

The Vertebrate Hearts and Genetic Basis of Human Cardiac Diseases

This book covers the exxential principles of genetics in a readable, accessible format using real-life examples of the way genes affect human behavior, health and illness, development and evolution.

This is a completely new way to think about human behavior. It explores why humans act the way that they do. Why is pedophilia normal? Why is there so much discrimination against women and girls? Why is religion? Why do people riot? What is wrong with being angry? Why do we lose control?

Lecture provides an overview of the progress made in molecular medicine applying genetics and genomics to the understanding, diagnosis, and treatment of human diseases. Specifically, the methods for identifying genes involved in human diseases are described. Examples from 10 genes and diseases will be provided, drawing on the author's research. Topics include examples from simple Mendelian diseases, such as cystic fibrosis, inherited cancers, oncogenes activated by chromosomal translocations, host genes involved in infectious disease, genes identified via genomewide association studies, pathogens causing cancer, and gene families contributing to multiple diseases. For each example, historical details will be provided as background for readers to understand the context and process of the discoveries, technologies explained, and current understanding and treatment implications detailed.

Genetic Basis of Human Oral Inflammatory Disease

The Neurostructural and Genetic Basis of Human Values

Human Genetics

Development and Reproduction in Humans and Animal Model Species

Genetic Basis for Respiratory Control Disorders

This book provides a comprehensive compilation of the evidence available regarding the role of genetic differences in the etiology of human obesities and their health and metabolic implications. It also identifies the most promising research areas, methods, and strategies for use in future efforts to understand the genetic basis of obesities and their consequences on human health. Leading researchers in their respective fields present contributed chapters on such topics as etiology and the prevalence of obesities, nongenetic determinants of obesity and fat topography, and animal models and molecular biological technology used to delineate the genetic basis of human obesities. A major portion of the book is devoted to human genetic research and clinical observations encompassing adoption studies, twin studies, family studies, single gene effects, temporal trends and etiology heterogeneity, energy intake and food preference, energy expenditure, and susceptibility to metabolic derangements in the obese state. Future directions of research in the field are covered in the book as well.

The basis of the morphological and behavioral differences between humans and other animals have been studied since antiquity. However, the genetic basis for these human-specific traits remains poorly understood. Recent computational screens to identify different classes of promising genomic regions have highlighted regions that are selectively deleted in humans, regions that experience accelerated substitution rates in humans, and regions that are unique to humans. Although reporter assays suggest that some of these genomic regions may act as enhancers, little is known about how specific genomic changes affect cellular or organismal phenotypes. In my dissertation research, I have attempted to identify and understand genomic regions that underlie human evolution using two different approaches: (1) interrogating the function of specific genomic regions that were identified in prior computational screens; and (2) developing an experimental model system that would allow for the genetic dissection of human and chimpanzee differences within the same cell. I have focused much of my doctoral research on one particular human-specific insertion, a tandem repeat located intronic to CACNA1C, which encodes the pore-forming alpha subunit of the L-type voltage-gated calcium channel CaV1.2. We find that this human-specific tandem repeat is much larger than the size annotated in the human reference genome, is closely linked to SNPs associated with bipolar disorder and schizophrenia, and acts as an enhancer in vitro. Strikingly, different human alleles linked to either the protective-associated or risk-associated psychiatric disease SNPs display differential enhancer activity. We observe that this mirrors differences seen in CACNA1C expression in previous studies, suggesting that this human-specific insertion may play a critical role in both human evolution and human disease. To further investigate its function, we are now modeling this human-specific tandem repeat in mice and in brain organoids. In ongoing work, we have identified striking transcriptomic and calcium signaling changes in these models. I have also investigated a human-specific deletion that is located in the intergenic region between MET and CAV1. In initial experiments, we have examined lacZ reporter expression at E18.5 in the mouse and performed RNA sequencing at E14.5 and P28 in different brain regions in mice where this human-specific deletion has been recapitulated. Additional work is needed to follow-up on these preliminary results. Lastly, I have worked to develop a model system that would allow for unbiased experimental screens for genomic regions that underlie human evolution. We have fused human and chimpanzee iPSC lines to generate tetraploid lines that contain both the human and the chimpanzee diploid genomes (allo-tetraploids). We have also generated auto-tetraploids (same-species) and shown that these auto-tetraploid iPSC lines are very similar to diploid iPSC lines at the transcriptional level, suggesting that the tetraploid iPSC system may be suitable to uncover genetic differences between humans and chimpanzees. Using RNA sequencing, we have identified genes whose expression is controlled in cis or trans between humans and chimpanzees in iPSCs. We have also explored methods to induce mitotic recombination between human and chimpanzee chromosomes within tetraploid iPSC lines using small molecules and CRISPR, respectively. Future work to fully establish mitotic recombination workflows will allow us to map traits that differ between human and chimp cell lines to specific genomic regions.

Ultimately, the quality of the tools available for genetic analysis and experimental disease models will be assessed on the basis of whether they provide new information that generates novel treatments for human disease. In addition, the time frame in which genetic discoveries impact clinical practice is also an important dimension of how society assesses the results of the significant public financial investment in genetic research. Because of the investment and the increased expectation that new tre- ments will

be found for common diseases, allowing decades to pass before basic discoveries are made and translated into new therapies is no longer acceptable. Computational Genetics and Genomics: Tools for Understanding Disease provides an overview and assessment of currently available and developing tools for genetic analysis. It is hoped that these new tools can be used to identify the genetic basis for susceptibility to disease. Although this very broad topic is addressed in many other books and journal articles, Computational Genetics and Genomics: Tools for Understanding Disease focuses on methods used for analyzing mouse genetic models of biomedically - portant traits. This volume aims to demonstrate that commonly used inbred mouse strains can be used to model virtually all human disea- related traits. Importantly, recently developed computational tools will enable the genetic basis for differences in disease-related traits to be rapidly identified using these inbred mouse strains. On average, a decade is required to carry out the development process required to demonstrate that a new disease treatment is beneficial.

Computational Challenges in Genomic Analysis for the Discovery of the Genetic Basis of Human Disease

Genetics of Fitness and Physical Performance

Are We Hardwired?

From Gene to Therapy

The Genetic Basis of Human Height

Bringing together top-level contributions on all aspects of the subject, this book provides an overview of the recent advances in the genetics of respiratory control in health and disease. It also shows how combined studies in humans and mouse models have helped to improve our understanding of the mechanisms that underlie genetically determined respiratory control disorders with the goal of developing new therapeutic interventions.

Reveals what leading experts have recently discovered about cancers caused by DNA alterations! The second edition of THE GENETICS OF CANCER, newly titled THE GENETIC BASIS OF HUMAN CANCERS, updates and informs on the most recent progress in genetic cancer research and its impact on patient care. With contributions by the foremost authorities in the field, this fascinating new edition reports on how to understand and predict tumor development - information that can enhance decision-making and advance genetic research. 2ND Edition Highlights NEW CHAPTERS: * Peutz-Jeghers syndrome * Juvenile polyposis syndrome * Tumor genome instability * Gene expression profiling in cancer * Pilomatricoma and pilomatrix carcinoma * Hereditary paragangliomas of the head and neck * Cylindromatosis * Familial cardiac myxomas and carney complex * Cancers of the oral cavity and pharynx * Genetic abnormalities in lymphoid malignancies THOROUGHLY REVISED: * Every chapter has been meticulously reviewed and revised to incorporate the most recent research and clinical findings * Includes a valuable introduction by renowned editors Vogelstein & Kinser* Features 150 MORE illustrations than the previous edition

The ATP-binding cassette (ABC) transporter genes are ubiquitous in the genomes of all vertebrates so far studied. The human ABC transporter superfamily contains 48 genes, subdivided into 7 subfamilies ranging from A to G (based on sequence homology of their nucleotide binding domains). The ABC proteins encoded by these genes are ATP-driven transmembrane pumps, some of which possess the capacity to efflux harmful toxic substances and therefore play a key role in xenobiotic defense. ABC proteins have been evolutionarily conserved from bacteria to humans and multiple gene duplication and deletion events in the ABC genes indicate that the process of gene evolution is still ongoing. Polymorphisms and variations in these genes are linked to variations in expression, function, drug disposition, and drug response. Single nucleotide polymorphisms (SNPs) in these genes could be markers of individual risk for adverse drug reactions or susceptibility to complex diseases. The pharmacogenetics of this unique family of transporters is still under study; however, in the context of human health, it is a well-known fact that variations in these transporters are the underlying cause for several human diseases including cystic fibrosis, Pseudoxanthoma elasticum (PXE), and X-linked adenoleukodystrophy (X-ALD). Table of Contents: Introduction to the Human ATP-Binding Cassette (ABC) Transporter Superfamily / Evolution of ABC Transporters / Overview of ABC Transporters in Human Disease / The Cystic Fibrosis Transmembrane Conductance Regulator-ABCC7 / PXE / X-linked Adrenoleukodystrophy / ABC Proteins: A Global Perspective / References / Titles of Related Interest

Genetic Basis of Society

Why War?

The Genetics of Obesity

ABC Transporters in Human Disease

Effects of Recent Evolution on the Genetic Basis of Human Disease

This book describes human development including sexual reproduction and stem cell research with the development of model organisms that are accessible to genetic and experimental analysis in readily understandable texts and 315 multi-colored graphics. The introductory account of model organisms selected from the entire animal kingdom presents general principles, which are then outlined in subsequent chapters devoted to, for example, sexual development; genes controlling development and their contemporary molecular-analysis methods; production of clones and transgenic animals; development of the nervous and circulatory systems; regenerative medicine and ageing. Finally the evolution of developmental toolkits and novelties is

discussed including the genetic basis of the enlargement of the human forebrain. Separate boxes are devoted to controversial questions such as the benefits and problems of prenatal diagnostics or the construction of ancient body plans.

Why War? An Inquiry into the Genetic and Social Sources of Human Warfare Humanity seems to be its own worst enemy. Why War? explores the biological and social imperatives for humans to wage war. From the most primitive societies to the most advanced nations, humans are driven by genetic, neurological and hormonal forces to kill their fellow humans in wars. They kill those who are not like them, whose skin is of a different color, who believe in a different religion than theirs, and those who are governed in a different way than they are. Only disease and old age kill more people than war. Dr. Pitman brings that perspective to describe the evidence of a genetic basis of racial and ethnic xenophobia that has triggered many wars; why many soldiers find pleasure in war and are willing to risk their lives and sacrifice themselves for their county, religion or ethnic group; and why societies are willing to sacrifice their young men and women in war. Increasingly, nations, religious and ethnic groups have become caught up with the fever of war, ready to risk their existence to gain power and to right imagined wrongs. Today, peace seems more difficult to achieve than ever before. George R. Pitman is retired from the US Arms Control and Disarmament Agency and the US State Department. He has devoted the last twelve years to studying the genetic, physiological and social bases of human warfare. Pitman has been interested in why humans are so warlike since he was a child listening tp the radio announcements about the invasions of Czechoslovakia and Austria and the outbreak of World War II. He holds a PhD in physics, has studied international relations at UCLA, and evolutionary biology and the anthropology of war. Pitman has authored papers on the issues of war and peace, as well as writing Neither War nor Peace: A History of the Cold War and of Strategic Arms Control.

Aims to identify genes involved in craniosynostosis and to characterize mutations of these genes.

A Journey Through Genetics

Understanding Human Disease through Genetics

The Genetic Basis of Human Cancer

Methods for the Quantitative Characterization of the Genetic Basis of Human Complex Traits

The Genetic Basis of Human Mammary Cancer

Epilepsy affects approximately 3% of the population, and is usually defined as a tendency to experience recurrent seizures arising from periodic neuronal hyperexcitability of unknown causes. Different genetic factors, through various mechanisms, can cause this abnormal neuronal behavior. The etiology of epilepsy is a major determinant of clinical course and prognosis. Many of the genes that have been implicated in idiopathic epilepsies code for ion channels, whereas a wide spectrum of syndromes where epilepsy is a main clinical feature are caused by mutated genes that are involved in functions as diverse as cortical development, brain malformations, mitochondrial function, and cell metabolism. Similarly, different conditions as hypoxia, trauma, infections, or metabolic unbalances can develop epileptic syndromes where upregulation of several genes could be related to the epileptogenic mechanisms. The most common human genetic epilepsies display a complex pattern of inheritance, and the susceptible genes are largely unknown. However, major advances have recently been made in our understanding of the genetic basis of monogenic inherited epilepsies. As we continue to unravel the molecular genetic basis for epilepsies, it will increasingly influence their classification and diagnosis. A majority of epileptic patients may control their crisis with anticonvulsant drugs, however 30%-40% became refractory to pharmacological therapies and require surgical treatment. The challenge of the molecular revolution will be the design of the best treatment protocols based on genetic profiles that include both the specific mechanistic etiology of the epilepsies, as well as their potential refractory behavior to current medications. This includes also the design of new therapeutic agents and targets, so as to reduce the number of cases with refractory epilepsy and epileptogenesis, and perhaps avoid the current surgical treatment (a procedure that was first described more than 4000 years ago) except as a last option.

Recent technological advances in the field of molecular biology have ushered in the genome wide association era of human genetics. Researchers can now simultaneously examine hundreds of thousands of single nucleotide polymorphisms (SNPs) in an individual at continually decreasing costs. In an effort to characterize distributions of SNPs in human populations a set of four million SNPs was collected in 269 individuals from four populations. This HapMap data set in combination with high throughput genotyping technology has caused a fundamental shift in the methodologies of scientists searching for the relationship between genotype and phenotype. The genome wide association study (GWAS) has become mainstream practice, leading to the discovery of a growing number of loci associated with the genetics basis of complex phenotypes including many human diseases. This work describes novel methods, resources, tools, and techniques designed to improve our ability to interpret and utilize GWAS and HapMap data. The Weighted Haplotype (WHAP) association method leverages the linkage structure information from the HapMap to improve GWAS power by providing accurate statistics for unobserved SNPs without the costs of additional genotyping. The SAT based tagging algorithm SATTagger identifies which SNPs to genotype as part of an association study, and provides the first optimal genome wide solution to this classic bioinformatics problem. The HapMap suffers from the fundamental limitation that at most 60 unrelated individuals are available per population. An analytical framework for analyzing the implications of a finite sample HapMap is presented. The results of the first round of GWAS studies showed that effect sizes of causal variants were small and that larger sample sizes were required for adequate power. Meta-analysis provides a mechanism for overcoming this problem with the cost of additional genotyping. A new statistic for imputation based meta analysis in a GWAS is given. Additional research is presented on MHC Class II binding prediction, which is a useful tool in understanding auto-immune and pathogenic diseases. A physics based binding model is presented with an EM like solution to find the optimal binding conformation.

“A Journey Through Genetics Part II” is designed to continue on the incredible journey initiated in Part I to explore the exciting discoveries in genetics and molecular biology. In Part I, the reader embarked on a genetic odyssey that started with the “Father of Genetics,” Gregor Mendel, and culminated in the invention of one of the most powerful tools in molecular biology—the polymerase chain reaction. The second part of the book will take the reader on a journey to explore the frontiers of genetic diversity, gene cloning, the human journey, and the human genome project! The book

is targeted toward undergraduate non-majors and also as a “companion” to a standard genetics textbook for biology majors. The book will also prove to be useful for anyone that wants to understand the stories behind the science of genetics.

The Genetic Basis of Male Infertility

Tools for Understanding Disease

The Genetic Basis of Human Pancreatic Developmental Abnormalities

The Genetic Basis for Human Disease

The Genetic Basis of Abnormal Human Behavior

A major finding from the last decade of genome-wide association studies (GWAS) is that variant-phenotype associations are significantly enriched in noncoding regulatory regions of the genome. This result suggests that GWAS associations localize variants that modulate phenotype via gene regulation as opposed to alterations in protein structure/function. However, for most complex traits, most aspects of genetic architecture-the number of causal variants/genes for a trait and the degree to which causal effect sizes are coupled with genomic features such as minor allele frequency (MAF) and linkage disequilibrium (LD)-remain actively debated. In this dissertation, I introduce three new methods to explore and quantitatively characterize complex-trait genetic architecture. First, I derive an unbiased estimator of genome-wide SNP-heritability under a very general random effects model that makes minimal assumptions on the underlying (unknown) genetic architecture of the trait. Second, I introduce a method for estimating the number of causal variants that are shared between two ancestral populations for a given trait, and I discuss the implications of the method and real-data results for improving polygenic risk prediction in ethnic minority populations. Third, I propose methods for partitioning the heritability of individual genes by MAF to identify disease-relevant genes, with the hypothesis that some disease-relevant genes may have relatively large heritability contributions from rare and low-frequency variants while still having low total gene-level heritability.

Human Genetics provides an insight into the basic human genetics, common genetic disorders, the inheritance pattern, the genetic basis for the diseases, the sensitive periods in human development, the detection of the diseases and the mechanism of genetic variation and deals with the heritable nature of most of the diseases. This book highlights the human genome project with its social implications. The proposed model for human cloning and stem cells as 21st century medicine for genetic diseases and describes the process of genetic counseling and the treatment methods undertaken in dealing with the genetic disorders. The ethical issues related to genetic counseling are also presented.

In the last 100,000 years, humans have been subjected to multiple different evolutionary pressures. Migration events, changing food sources, climate change, and technological advances are some of the ways environmental changes have applied pressure on human populations to undergo change. Recent advances in methods to measure differences in DNA sequences have led to new powerful techniques to measure the effect of evolution on different human populations. Also due to the availability of recent explosion of genomic data, our understanding of genetic basis of human disease has grown significantly. However, our knowledge regarding the effect that recent evolution has had on the genetic susceptibility to disease has grown to a much lesser extent. There is a lack of studies attempting to place the genetic basis of disease in the context of recent evolutionary changes. I describe multiple ways in which recent evolutionary pressures on the human genome can lead to insights to understanding how evolution has impacted complex disease. I show that GWAS (Genome-Wide Association Studies) are particularly well suited to measure the effect of recent evolution in complex disease. I provide methodology to detect positive selection in human disease and are able to ascertain whether recent evolution has disproportionately increased or decreased the risk of inherited disease. In addition, I introduce a method to approximate when and where genetic risk differentiation for specific disease has occurred, starting when humans began migration out of Africa. Environmental changes in the last 10,000 years known to have created novel, diverse, and pervasive pathogens. I provide methodology to find positive selection in communicable disease. I identify populations that have most likely been severely impacted by specific pathogens in recent human history. I develop and apply methods to identify specific genetic variants important to both communicable and inherited disease that have been affected by evolutionary pressures. I find that type 1 diabetes has recently undergone strong positive selection towards increasing genetic risk in European derived populations. In addition type 2 diabetes and pancreatic cancer is associated with migration trajectories and I find genetic risk differentiation exceeding what is expected by genetic drift in a total of 11 complex diseases. Finally, I find evidence of positive selection in many distinct populations within proteins interacting bacillus anthracis and yersinia pestis, which cause anthrax and the bubonic plague, respectively. I have shown how recent evolution can lead to an increased understanding of both inherited and infectious disease.

Investigating the Genetic Basis of Human Evolution

The Genetic Basis of Human Disease

An Inquiry Into the Genetic and Social Foundations of Human Warfare

The Genetic Basis of Human Craniosynostosis Syndromes

Quantifying the Genetic Basis of Antigenic Variation Among Human Influenza A Viruses