

Genetic Dissection of Complex Traits

Eric S. Lander* and Nicholas J. Schork

Medical genetics was revolutionized during the 1980s by the application of genetic mapping to locate the genes responsible for simple Mendelian diseases. Most diseases and traits, however, do not follow simple inheritance patterns. Geneticists have thus begun taking up the even greater challenge of the genetic dissection of complex traits. Four major approaches have been developed: linkage analysis, allele-sharing methods, association studies, and polygenic analysis of experimental crosses. This article synthesizes the current state of the genetic dissection of complex traits—describing the methods, limitations, and recent applications to biological problems.

Human genetics has sparked a revolution in medical science on the basis of the seemingly improbable notion that one can systematically discover the genes causing inherited diseases without any prior biological clue as to how they function. The method of genetic mapping, by which one compares the inheritance pattern of a trait with the inheritance patterns of chromosomal regions, allows one to find where a gene is without knowing what it is. The approach is completely generic, being equally applicable to spongiform brain degeneration as to inflammatory bowel disease.

To geneticists, this revolution is really nothing new. Genetic mapping of trait-causing genes to chromosomal locations dates back to the work of Sturtevant in 1913 (1). It has been a mainstay of experimental geneticists who study fruit flies, nematode worms, yeast, and maize and who developed genetic maps containing hundreds of genetic markers that made it possible to follow the inheritance of any chromosomal region in a controlled cross. With the advent of recombinant DNA, genetic mapping was carried to its logical conclusion with the development of positional cloning—the isolation of a gene solely on the basis of its chromosomal location, without regard to its biochemical function. Positional cloning was invented by Bender and colleagues, who used it to isolate the *tithonus* complex in *Drosophila* (2), and it rapidly became a routine technique in flies and worms.

Despite its central role in experimental organisms, genetic mapping hardly figured in the study of humans throughout most of the century. There were two reasons: the lack of an abundant supply of genetic markers with which to study inheritance, and the inability

to arrange human crosses to suit experimental purposes. The key breakthrough was the recognition that naturally occurring DNA sequence variation provided a virtually unlimited supply of genetic markers—an idea first conceived of by Botstein and colleagues for yeast crosses (3) and subsequently for human families (4). With highly polymorphic genetic markers, one could trace inheritance in existing human pedigrees as if one had set up the crosses in the laboratory. These ideas soon led to an explosion of interest in the genetic mapping of rare human diseases having simple Mendelian inheritance. More than 400 such diseases have been genetically mapped in this manner, and nearly 40 have been positionally cloned (5).

Human geneticists are now beginning to explore a new genetic frontier, driven by an inconvenient reality: Most traits of medical relevance do not follow simple Mendelian monogenic inheritance. Such "complex" traits include susceptibilities to heart disease, hypertension, diabetes, cancer, and infection. The genetic dissection of complex traits is attracting many investigators with the promise of shedding light on old problems and is spawning a variety of analytical methods. The emerging issues turn out to be relevant not just to medical genetics, but to fundamental studies of mammalian development and applied work in agricultural improvement. The field is still at an early stage, but it is ready to explode much as it has done in recent years with the analysis of simple traits. The purpose of this article is to synthesize the key challenges and methods, to highlight some enlightening examples, and to identify further needs.

Complex Traits

The term "complex trait" refers to any phenotype that does not exhibit classic Mendelian recessive or dominant inheritance attributable to a single gene locus. In general, complexities arise when the simple correspondence between genotype and phenotype

breaks down, either because the same genotype can result in different phenotypes (due to the effects of chance, environment, or interactions with other genes) or different genotypes can result in the same phenotype.

To some extent, the category of complex traits is all-inclusive. Even the simplest genetic disease is complex, when looked at closely. Sickle cell anemia is a classic example of a simple Mendelian recessive trait. Yet, individuals carrying identical alleles at the β -globin locus can show markedly different clinical courses, ranging from early childhood mortality to a virtually unrecognized condition at age 50 (6). The trait of severe sickle cell anemia is thus complex, being influenced by multiple genetic factors including a mapped X-linked locus and an inferred autosomal locus that can increase fetal hemoglobin amounts and thereby partially ameliorate the disease (7).

It is often impossible to find a genetic marker that shows perfect cosegregation with a complex trait. The reasons for this can be ascribed to a few basic problems.

Incomplete penetrance and phenocopy. Some individuals who inherit a predisposing allele may not manifest the disease (incomplete penetrance), whereas others who inherit no predisposing allele may nonetheless get the disease as a result of environmental or random causes (phenocopy). Thus, the genotype at a given locus may affect the probability of disease, but not fully determine the outcome. The penetrance function $f(G)$, specifying the probability of disease for each genotype G , may also depend on nongenetic factors such as age, sex, environment, and other genes. For example, the risk of breast cancer by ages 40, 55, and 60 is 37%, 66%, and 85% in a woman carrying a mutation at the *BRCA1* locus as compared with 0.4%, 3%, and 8% in a noncarrier (8). In such cases, genetic mapping is hampered by the fact that a predisposing allele may be present in some unaffected individuals or absent in some affected individuals.

Genetic (or locus) heterogeneity. Mutations in any one of several genes may result in identical phenotypes, such as when the genes are required for a common biochemical pathway or cellular structure. This poses no problem in experimental organisms, because geneticists can arrange to work with pure-breeding strains and perform crosses to assign mutations to complementation classes. In contrast, medical geneticists typically have no way to know whether two patients suffer from the same disease for

E. S. Lander is with the Whitehead Institute for Biomedical Research, Cambridge, MA 02142, USA, and the Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA. N. J. Schork is with the Department of Genetics and Center for Human Genetics, Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH 44106, USA.

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Genetic Dissection Of Complex Traits

Chao Zhang



Genetic Dissection Of Complex Traits:

Genetic Dissection of Complex Traits D.C. Rao, C. Charles Gu, 2008-04-23 The field of genetics is rapidly evolving and new medical breakthroughs are occurring as a result of advances in knowledge of genetics This series continually publishes important reviews of the broadest interest to geneticists and their colleagues in affiliated disciplines Five sections on the latest advances in complex traits Methods for testing with ethical legal and social implications Hot topics include discussions on systems biology approach to drug discovery using comparative genomics for detecting human disease genes computationally intensive challenges and more The Genetic Dissection of Complex Traits Christy Myrick, 1998

The Genetic Dissection of Complex Traits Stephen Lister Lake, 2002 **Advances in Statistical Methods for the Genetic Dissection of Complex Traits in Plants** Yuan-Ming Zhang, Zhenyu Jia, Shang-Qian Xie, Jia Wen, Shibo Wang, Ya-Wen Zhang, 2024-01-26 Genome wide association studies GWAS have been widely used in the genetic dissection of complex traits However there are still limits in current GWAS statistics For example 1 almost all the existing methods do not estimate additive and dominance effects in quantitative trait nucleotide QTN detection 2 the methods for detecting QTN by environment interaction QEI are not straightforward and do not estimate additive and dominance effects as well as additive by environment and dominance by environment interaction effects leading to unreliable results and 3 no or too simple polygenic background controls have been employed in QTN by QTN interaction QQI detection As a result few studies of QEI and QQI for complex traits have been reported based on multiple environment experiments Recently new statistical tools including 3VmrMLM have been developed to address these needs in GWAS In 3VmrMLM all the trait associated effects including QTN QEI and QQI related effects are compressed into a single effect related vector while all the polygenic backgrounds are compressed into a single polygenic effect matrix These compressed parameters can be accurately and efficiently estimated through a unified mixed model analysis To further validate these new GWAS methods particularly 3VmrMLM they should be rigorously tested in real data of various plants and a wide range of other species The Applications of New Multi-Locus GWAS Methodologies in the Genetic Dissection of Complex Traits Yuan-Ming Zhang, Zhenyu Jia, Jim M Dunwell, 2019-06-19 Genome Wide Association Studies GWAS are widely used in the genetic dissection of complex traits Most existing methods are based on single marker association in genome wide scans with population structure and polygenic background controls To control the false positive rate the Bonferroni correction for multiple tests is frequently adopted This stringent correction results in the exclusion of important loci especially for GWAS in crop genetics To address this issue multi locus GWAS methodologies have been recommended i e FASTmrEMMA ISIS EM BLASSO mrMLM FASTmrMLM pLARmEB pKWmEB and FarmCPU In this Research Topic our purpose is to clarify some important issues in the application of multi locus GWAS methods Here we discuss the following subjects First we discuss the advantages of new multi locus GWAS methods over the widely used single locus GWAS methods in the genetic dissection of complex traits

metabolites and gene expression levels Secondly large experiment error in the field measurement of phenotypic values for complex traits in crop genetics results in relatively large P values in GWAS indicating the existence of small number of significantly associated SNPs To solve this issue a less stringent P value critical value is often adopted i e $0.001/0.0001$ and $1/m$ is the number of markers Although lowering the stringency with which an association is made could identify more hits confidence in these hits would significantly drop In this Research Topic we propose a new threshold of significant QTN LOD 3.0 or P value 2.0×10^{-4} in multi locus GWAS to balance high power and low false positive rate Thirdly heritability missing in GWAS is a common phenomenon and a series of scientists have explained the reasons why the heritability is missing In this Research Topic we also add one additional reason and propose the joint use of several GWAS methodologies to capture more QTNs Thus overall estimated heritability would be increased Finally we discuss how to select and use these multi locus GWAS methods

Genetic Dissection of Complex Traits Pankaj Sharma,1998 *Development of Variance Component Methods for Genetic Dissection of Complex Traits*,2009 - □□□□□□□□ □□□□□□ □□□□□□ □□□□□□ □□□□□□ □□ □□□□ □□□□□□

□□□□□□ □□□□□□□□□□ Sagiv Shifman,2004 **Phenomics Enabled Genetic Dissection of Complex Traits in Wheat Breeding** Daljit Singh,2018 A central question in modern biology is to understand the genotype to phenotype G2P link that is how the genetics of an organism results in specific characteristics However prediction of phenotypes from genotypes is a difficult problem due to the complex nature of genomes the environment and their interactions While the recent advancements in genome sequencing technologies have provided almost unlimited access to high density genetic markers large scale rapid and accurate phenotyping of complex plant traits remains a major bottleneck Here we demonstrate field based complex trait assessment approaches using a commercially available light weight Unmanned Aerial Systems UAS By deploying novel data acquisition and processing pipelines we quantified lodging ground cover and crop growth rate of 1745 advanced spring wheat lines at multiple time points over the course of three field seasons at three field sites in South Asia High correlations of digital measures to visual estimates and superior broad sense heritability demonstrate these approaches are amenable for reproducible assessment of complex plant traits in large breeding nurseries Using these validated high throughput measurements we applied genome wide association and prediction models to assess the underlying genetic architecture and genetic control Our results suggest a diffuse genetic architecture for lodging and ground cover in wheat but heritable genetic variation for prediction and selection in breeding programs The logistic regression derived parameters of dynamic plant height exhibited strong physiological linkages with several developmental and agronomic traits suggesting the potential targets of selection and the associated tradeoffs Taken together our highly reproducible approaches provide a proof of concept application of UAS based phenomics that is scalable to tens of thousands of plots in breeding and genetic studies as will be needed to understand the G2P and increase the rate of gain for complex traits in crop breeding

Molecular Genetic Dissection of Complex Traits in White Clover Charlotte Jones,2005 *An Integrated Approach for the Genetic*

Dissection of Complex Traits in Yeast Gal-Hagit Romano,2009 **Molecular Dissection of Complex Traits** Andrew H. Paterson,2019-09-17 In the past 10 years contemporary geneticists using new molecular tools have been able to resolve complex traits into individual genetic components and describe each such component in detail *Molecular Dissection of Complex Traits* summarizes the state of the art in molecular analysis of complex traits QTL mapping placing new developments in this *Bioinformatics Tools for the Genetic Dissection of Complex Traits in Chickens* Claudia Paola Cabrera Cárdenas,D. J. de Koning,Chris Haley,Andy Law,2009 This thesis explores the genetic characterization of the mechanisms underlying complex traits in chicken through the use and development of bioinformatics tools The characterization of quantitative trait loci controlling complex traits has proven to be very challenging This thesis comprises the study of experimental designs annotation procedures and functional analyses These represent some of the main bottlenecks involved in the integration of QTLs with the biological interpretation of high throughput technologies The thesis begins with an investigation of the bioinformatics tools and procedures available for genome research briefly reviewing microarray technology and commonly applied experimental designs A targeted experimental design based on the concept of genetical genomics is then presented and applied in order to study a known functional QTL responsible for chicken body weight This approach contrasts the gene expression levels of two alternative QTL genotypes hence narrowing the QTL phenotype gap and giving a direct quantification of the link between the genotypes and the genetic responses Potential candidate genes responsible for the chicken body weight QTL are identified by using the location of the genes their expression and biological significance In order to deal with the multiple sources of information and exploit the data effectively a systematic approach and a relational database were developed to improve the annotation of the probes of the ARK Genomics G gallus 13K v4 0 cDNA array utilized on the experiment To follow up the investigation of the targeted genetical genomics study a detailed functional analysis is performed on the dataset The aim is to identify the downstream effects through the identification of functional variation found in pathways and secondly to achieve a further characterization of potential candidate genes by using comparative genomics and sequence analyses Finally the investigation of the body weight QTL syntenic regions and their reported QTLs are presented **Genetic Dissection of Important Traits in Aquaculture: Genome-scale Tools Development, Trait Localization and Regulatory Mechanism Exploration** Peng Xu,Lior David,Paulino Martinez,Gen Hua Yue,2020-07-31 **The Molecular Pathology of Autoimmune Diseases** Argyrios N Theofilopoulos,Constantin A. Bona,2002-12-06 Remarkable advances have been made in the pathogenesis of autoimmunity such as with bone marrow transplantation which is becoming a powerful strategy in treating certain life threatening diseases *The Molecular Pathology of Autoimmune Diseases* is a concise and centralized resource for information on the topic with a special focus on the molecular and genetic basis of these disorders Dozens of international experts devote themselves to illuminating the reader in this volume with discussions on the basic aspects of autoimmune processes to systemic and organ specific diseases This

volume is an invaluable reference to students and professionals in immunology and related fields **Biological Shape**

Analysis - Proceedings Of The 3rd International Symposium Pete E Lestrel, 2015-06-11 The proceedings were designed to bring together researchers who share a common interest in the quantitative description of the biological form Participants came from very diverse disciplines such as agricultural genetics botany entomology forensics human anatomy paleontology human evolution primatology dentistry etc The participants applied various methodological approaches that are being increasingly used to describe aspects of the biological form These techniques include neural networks Fourier descriptors shape mapping genome wide association studies GWAS Riemann curves surface mapping etc A number of the contributions in the proceedings represent state of the art research that reflects advances in that discipline Genetics of Common

Diseases Ian Day, Prof Steve Humphries, 2020-12-18 Many common diseases are partly attributable to the genes which an individual inherits Early steps have now been made in developing ways to determine which genetic variations are important with some recent successes This is a collection of papers from the Fifth Annual Molecular Pathology Symposium on the 10 December 1996 They represent the contributions to that meeting made by a set of distinguished scientists and clinicians whose work pertains to the furtherment of our understanding of the genetic components of common diseases and potential future approaches **Behavioral Genetics** Ronald A. Carson, Mark A Rothstein, 2003-05-22 Nine essays examining the

ethical cultural legal and biological underpinnings of behavioral genetics Scientists conducting human genome research are identifying genetic disorders and traits at an accelerating rate Genetic factors in human behavior appear particularly complex and slow to emerge yet are raising their own set of difficult ethical legal and social issues In Behavioral Genetics The Clash of Culture and Biology Ronald Carson and Mark Rothstein bring together well known experts from the fields of genetics ethics neuroscience psychiatry sociology and law to address the cultural legal and biological underpinnings of behavioral genetics The authors discuss a broad range of topics including the ethical questions arising from gene therapy and screening molecular research in psychiatry and the legal ramifications and social consequences of behavioral genetic information Throughout they focus on two basic concerns the quality of the science behind behavioral genetic claims and the need to formulate an appropriate ethically defensible response when the science turns out to be good This book is well written and stimulating The issues it raises are important for scientists and for those working in the legal and social services fields but they clearly also have relevance for everyone The New England Journal of Medicine This is the best introduction to behavioral genetics that I have read The varying viewpoints are presented with such clarity that this book should appeal to the general public and serve as a basic text for college courses Jay Katz Elizabeth K Dollard Professor Emeritus of Law Medicine and Psychiatry Harvey L Karp Professorial Lecturer in Law and Psychoanalysis Yale Law School *Genetics, Genomics and Breeding of Eucalypts* Robert J. Henry, 2014-07-08 Eucalypts are used for the production of paper products firewood charcoal potential feedstocks for bioenergy and biomaterials as ornamentals and landscape trees and in land

rehabilitation Eucalypt breeding is at an early stage with many plantings being only at the first stages of domestication The relatively small genomes of these species make the application of molecular genetics approaches attractive The application of modern genomics will accelerate the development of improved eucalypts for a wide range of uses This book brings together diverse information on the genetics genomics and breeding of these important forest species **Epilepsy** Jong Rho,Raman Sankar,Carl E. Stafstrom,2010-06-18 Epilepsy has afflicted humankind throughout recorded history yet it is only in the last half century that significant progress has been made in our basic understanding of the epileptic brain Pivotal advances in drug development and surgical techniques as well as the emergence of innovative approaches such as electrical stimulation of the nervo

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