New Trends in Clinical Genetics: Genomic Medicine

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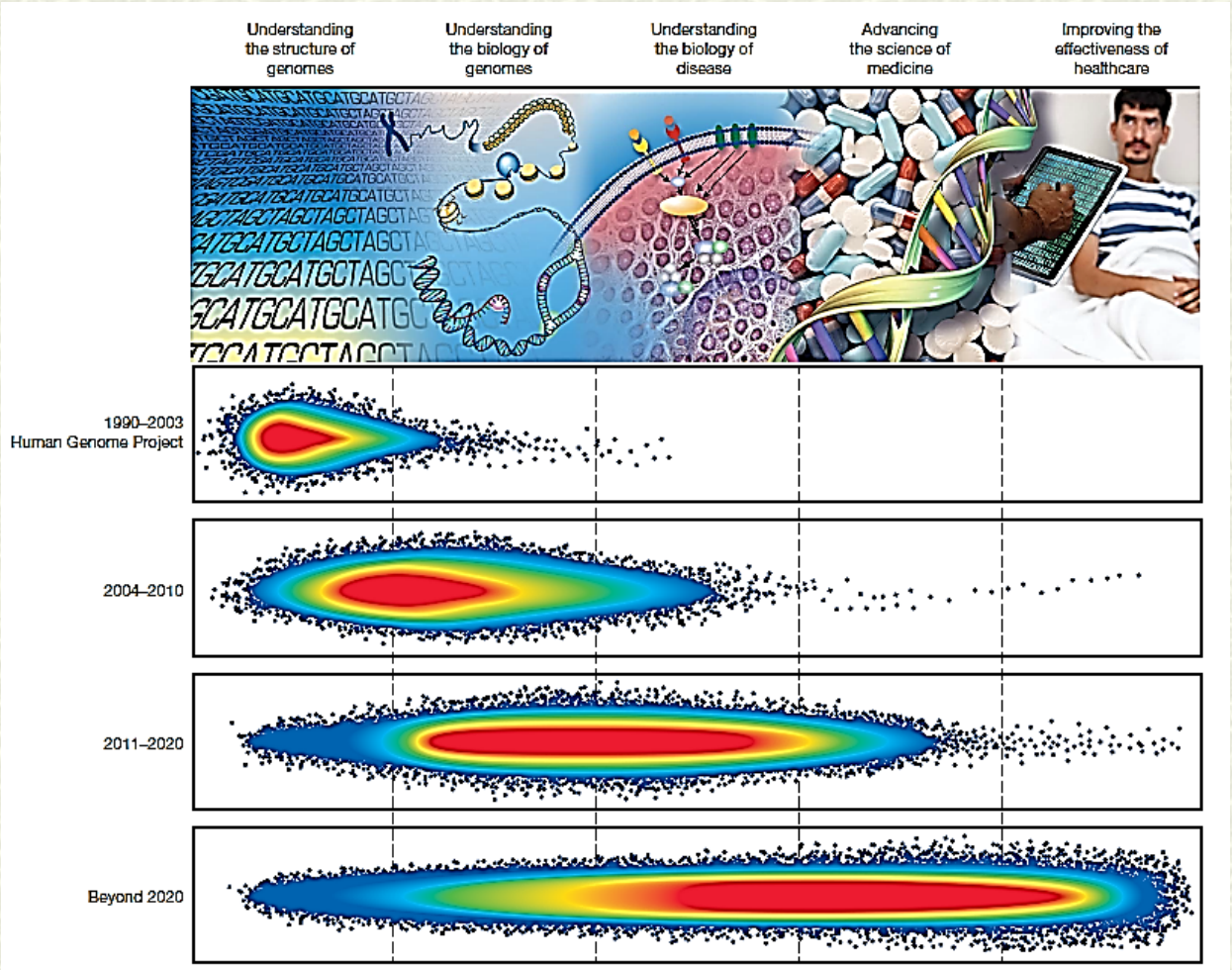
LF MU 2020

Genomic medicine: prediction



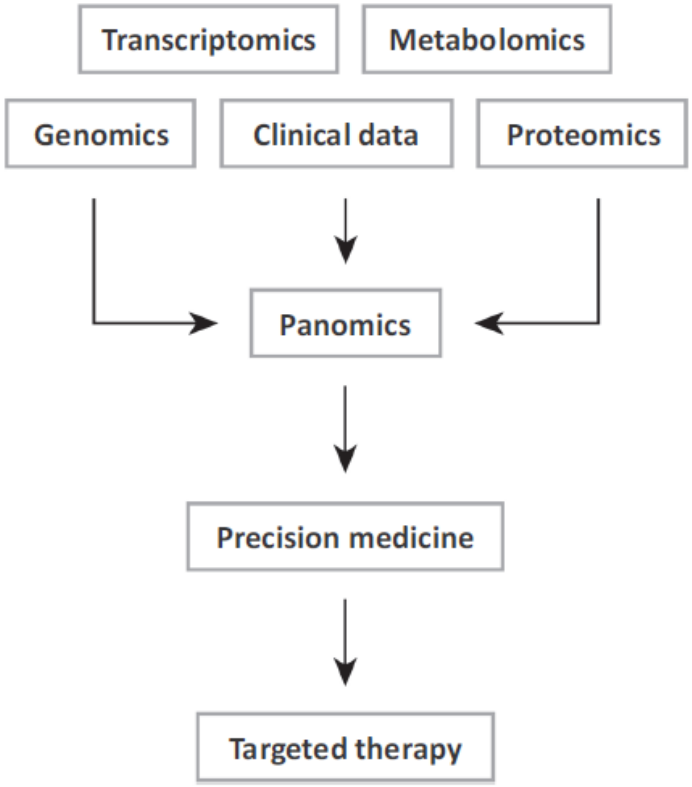
Charting a course for genomic medicine from base pairs to bedside

Green et al. 2011

204 | NATURE | VOL 470 | 10 FEBRUARY 2011

Top of your professional career

Precision medicine



Trends in Molecular Medicine

Figure 1. Proposed Model of Precision Medicine Approaches. Data from omic subfields are integrated (panomics) to guide patient care in a manner that accounts for the genetic variation of each patient.

Highlights

Genome sequencing costs are rapidly decreasing; within the coming decade we might anticipate that whole-genome sequencing may be affordable for patients.

Automated high-throughput DNA sequencing and peptide sequencing platforms are currently creating terabytes of information, referred to as 'big data'.

Big data are characterized by the three 'V's: a large volume of data, a high velocity of data production occurring in real time, and the variety of data that can encompass multiple omic subfields.

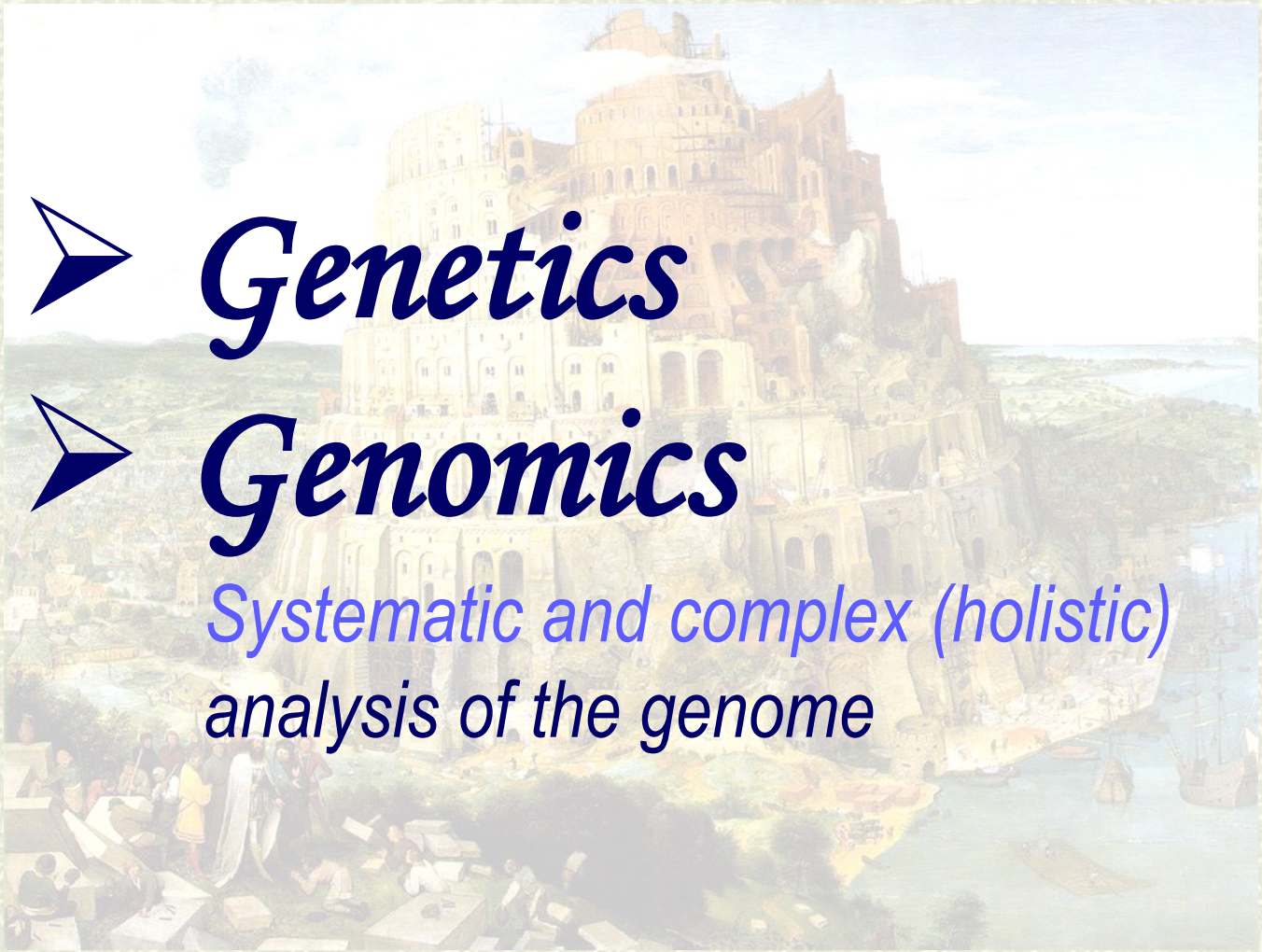
The analysis of big data has the potential to identify novel biomarkers of disease and targets for therapy. The analysis of large-scale datasets may enable the discovery of diagnostic or prognostic makers that are not readily apparent.

The complexity and vastness of data analysis may ultimately require the development of computational platforms to aid in the discovery of biological pathways underling health and disease.

Panomics for Precision M

Charanjit Sandhu,[1,*] Alia Qureshi,[2] and Andrew Emili[1]

Terminology: confusion of languages



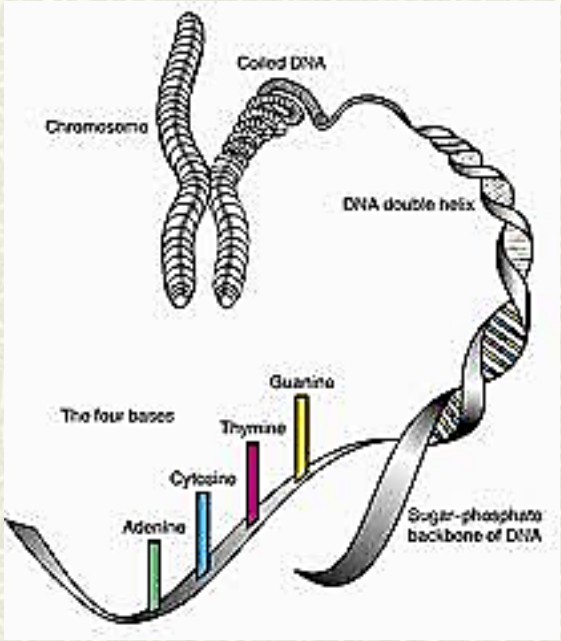
- *Genetics*
- *Genomics*

Systematic and complex (holistic)
analysis of the genome

Holistic approaches

Slide courtesy of Prof. Jamie McLeod, UK Lexington

Reminder: the GENOME



- > 1m DNA
- 24 chromosomes, mtDNA
- > 3,100,000,000 bp
- 20,000–25,000 protein coding genes (< 2% of the genome)
- > 5 MG SNPs
- „Junk“ DNA: RNA, repeats, ??

Holism and genomics:

Genome is more than the sum of its genes

1atgtgcccgc cgcgcggcct cctccttgtg gccatcctgg tcctcctaaa ccacctggac
61 cacctcagtt tggccaggaa cctccccaca gccacaccag gcccaggaat
gttccagtgc 121 ctcaaccact cccaaaacct gctgaggacc gtcagcaaca
cgcttcagaa ggccaggcaa 181 accctagaat tctactcctg cacttctgaa
gagatcgatc atgaggatat cacaaaagac 241 aagagcagca ccgtggcggc
ctgcctcccc ctggaactcg ccccgaacga gagttgcctg 301 gcttccagag
agatctcttt cataactaat gggagttgcc tgacccccgg aaaggcctct 361
tctatgatga cgctgtgcct tagcagcatc tatgaggact tgaagatgta ccaggtggag
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tctggatgag 481 aacatgctga cagccattga caagctgatg caggccctga
acttcaacag tgagactgtg 541 ccacaaaagc cctcccttga aggactggat
ttttataaaa ctaaagtcaa gctctgcatc 601 cttcttcatg ccttcagaat
ccgcgcagtg accatcaaca ggatgatggg ctatctgaat 661 gcttcctaa

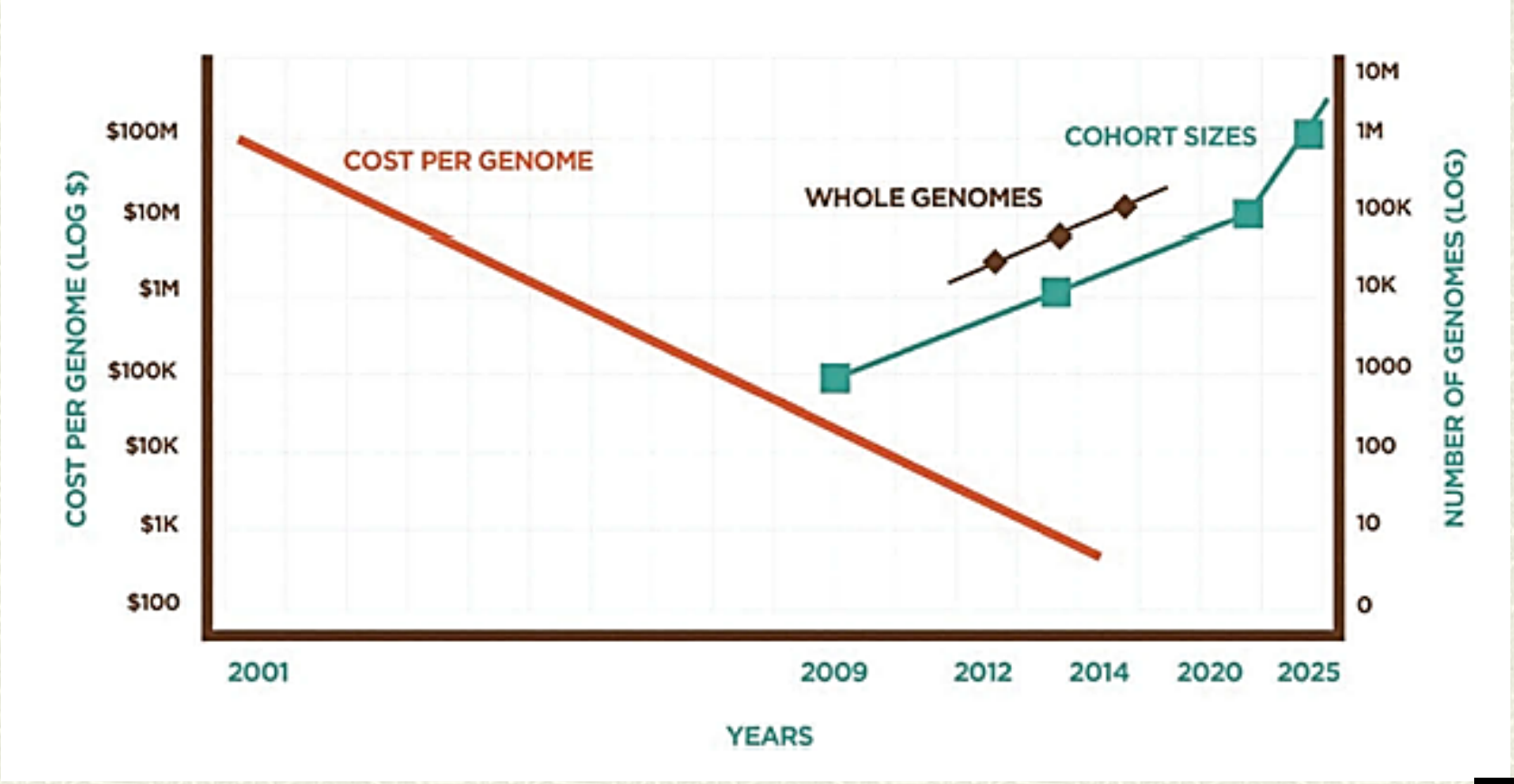
Postgenomic era

Full genome sequences determined (human genome 2001)

http://www.ncbi.nlm.nih.gov/Genomes/

Annotation of genomes

Genomic medicine - from theory to practice: financial aspects



Miniaturization and automation

Chips and arrays

Genomic medicine: clinical practice

Genetics inMedicine | REVIEW

Open

Implementing genomic medicine in the clinic: the future is here

Teri A. Manolio, MD, PhD[1], Rex L. Chisholm, PhD[2], Brad Ozenberger, PhD[1], Dan M. Roden, MD[3], Marc S. Williams, MD[4,5], Richard Wilson, PhD[6], David Bick, MD[7], Erwin P. Bottinger, MD[8], Murray H. Brilliant, PhD[9], Charis Eng, MD, PhD[10], Kelly A. Frazer, PhD[11], Bruce Korf, MD, PhD[12], David H. Ledbetter, PhD[5], James R. Lupski, MD, PhD[13], Clay Marsh, MD[14], David Mrazek, MD[15], Michael F. Murray, MD[16], Peter H. O'Donnell, MD[17], Daniel J. Rader, MD[18], Mary V. Relling, PharmD[19], Alan R. Shuldiner, MD[20], David Valle, MD[21], Richard Weinshilboum, MD[22], Eric D. Green, MD, PhD[1] and Geoffrey S. Ginsburg, MD, PhD[23]

Genomic medicine: clinical practice

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PERSPECTIVE

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Toward clinical genomics in everyday medicine: perspectives and recommendations

Susan K. Delaney[a], Michael L. Hultner[b†], Howard J. Jacob[c†], David H. Ledbetter[d†], Jeanette J. McCarthy[e†], Michael Ball[f], Kenneth B. Beckman[g], John W. Belmont[h], Cinnamon S. Bloss[i], Michael F. Christman[a], Andy Cosgrove[j*], Stephen A. Damiani[k,l], Timothy Danis[m], Massimo Delledonne[n], Michael J. Dougherty[o,p], Joel T. Dudley[q], W. Andrew Faucett[d], Jennifer R. Friedman[r], David H. Haase[s], Tom S. Hays[t], Stu Heilsberg[j*], Jeff Huber[u], Leah Kaminsky[v], Nikki Ledbetter[d], Warren H. Lee[w], Elissa Levin[q], Ondrej Libiger[x], Michael Linderman[q], Richard L. Love[m], David C. Magnus[y], AnneMarie Martland[x], Susan L. McClure[z], Scott E. Megill[aa], Helen Messier[ab], Robert L. Nussbaum[ac], Latha Palaniappan[ad], Bradley A. Patay[ae], Bradley W. Popovich[af], John Quackenbush[ag], Mark J. Savant[ah], Michael M. Su[ai], Sharon F. Terry[aj], Steven Tucker[ak], William T. Wong[al] and Robert C. Green[am†]

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An example:
Clinical Genome and Exome Sequencing (CGES)

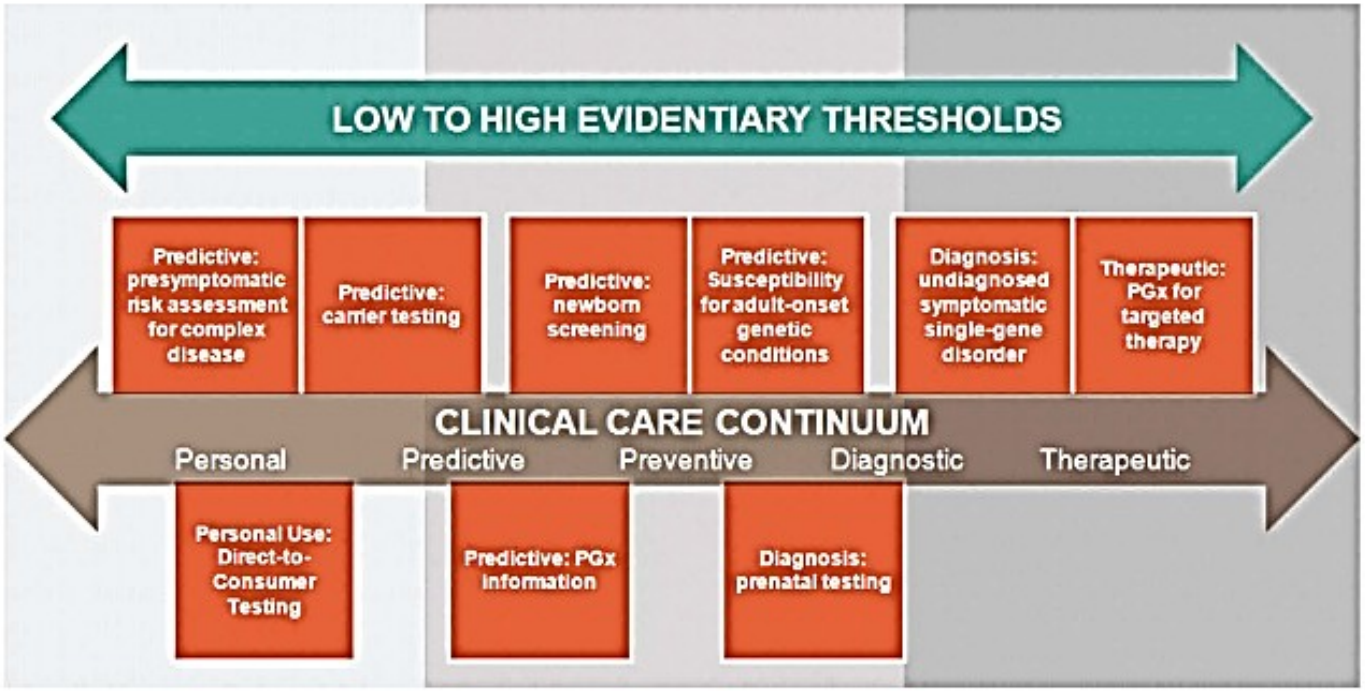

Figure 1. Defining CGES use cases along the clinical care continuum and appropriate evidentiary thresholds for each.

Examples of practical applications

Table 1. Summary of genetic testing.

Test type	Purpose description	Current example(s)
Diagnostic testing	To precisely identify a disease and assist in clinical decision-making	Creatine kinase (CK) level testing for Duchenne muscular dystrophy
Predictive testing	To predict the likelihood of developing a disease	*HTT* gene test for Huntington disease; *BRCA* gene testing for breast cancer
Carrier testing	To understand the likelihood of passing a genetic disease to a child	*CFTR* gene testing for cystic fibrosis
Prenatal testing	To identify disease in a fetus	Expanded alpha-fetoprotein (AFP) for risk of neural tube defects, such as spina bifida and Down syndrome
Newborn screening	To determine if a newborn has a disease known to cause problems in health and development	All states must screen for at least 21 disorders by law, and some states test for 30 or more. Metabolic (e.g. classic galactosemia (GALT)), endocrine (e.g. congenital hypothyroidism) and other disorders tested
Pharmacogenomics (PGx) testing	To determine the optimal drug therapy and dose given a person's metabolic response	The vitamin K epoxide reductase complex subunit 1 (*VKORC1*) test for likely response to the anticoagulant warfarin. *TPMT* gene testing for likely response to thiopurine immunosuppressive therapies
Research testing	To contribute to our understanding of underlying cause of disease	Genome-wide association studies (GWAS) to determine the association of a variant with a trait

Recommendations for health care providers

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Recommendations for the Integration of Genomics into Clinical Practice

Sarah Bowdin, M.D.[2], Adel Gilbert, M.S.[2], Emma Bedoukian, M.S.[3], Christopher Carew, M.B.A.[2], Margaret P Adam, M.D.[4], John Belmont, M.D., Ph.D.[5], Barbara Bernhardt, M.S.[6], Leslie Biesecker, M.D.[7], Hans T. Bjornsson, M.D., Ph.D.[8], Miriam Blitzer, Ph.D.[9], Lisa C. A. D'Alessandro, M.D.[28], Matthew A. Deardorff, M.D., Ph.D.[3,27], Laurie Demmer, M.D.[10], Alison Elliott, Ph.D.[11], Gerald L. Feldman, M.D., Ph.D.[12], Ian A. Glass, M.B.Ch.B., M.D.[4], Gail Herman, M.D., Ph.D.[13], Lucia Hindorff, Ph.D.[7], Fuki Hisama, M.D.[26], Louanne Hudgins, M.D.[14], A. Micheil Innes, M.D.[15], Laird Jackson, M.D.[16], Gail Jarvik, M.D., Ph.D.[26], Raymond Kim, M.D., Ph.D.[1], Bruce Korf, M.D., Ph.D.[17], David H. Ledbetter, Ph.D.[18], Mindy Li, M.D.[19], Eriskay Liston, M.S.[1], Christian Marshall, Ph.D.[25], Livija Medne, M.S.[3], M. Stephen Meyn, M.D., Ph.D.[1,2], Nasim Monfared, M.Sc.[1], Cynthia Morton, Ph.D.[20], John J. Mulvihill, M.D.[21], Sharon E. Plon, M.D., Ph.D.[29], Heidi Rehm, Ph.D.[20], Amy Roberts, M.D.[22], Cheryl Shuman, M.S.[1,2], Nancy B. Spinner, Ph.D.[19], D. James Stavropoulos, Ph.D.[25], Kathleen Valverde, M.S.[23], Darrel J. Waggoner, M.D.[24], Alisha Wilkens, M.S.[3], Ronald D. Cohn, M.D.[1,2,*], and Ian D. Krantz, M.D.[2,27,*]

Translating and realizing the comprehensive clinical benefits of genomic medicine remains a key challenge for the current and future care of patients. With the increasing application of CGES, it is necessary for geneticists and other health care providers to understand its benefits and limitations, in order to interpret the clinical relevance of genomic variants identified in the context of health and disease. Establishing new, collaborative working relationships with specialists across diverse

Genomic medicine:
Role of MDs in the process

- ✓ *Understanding of principles*
- ✓ *Medical interpretation of data*

Another example: genomic medicine and complex disease

Inherited diseases

- ✓ **Mendelian (OMIM)**

3000 loci

- ✓ **Complex**

900-1000 loci

Why complex disease?

Genomes in disease

- ✓ *0.6% chromosome abnormalities*
- ✓ *8% Mendelian diseases,*
- ✓ *90% Multifactorial disease,*
- ✓ *1.4% other than genetic problem*

Simple is not always simple

- ✓ *The same mutation in different genomes*
- ✓ *The same genome in different environments*
- ✓ *The same genome throughout ontogenesis*
- ✓ *The same genome with different microbiomes*

Really complex situations: different genomes in different environments

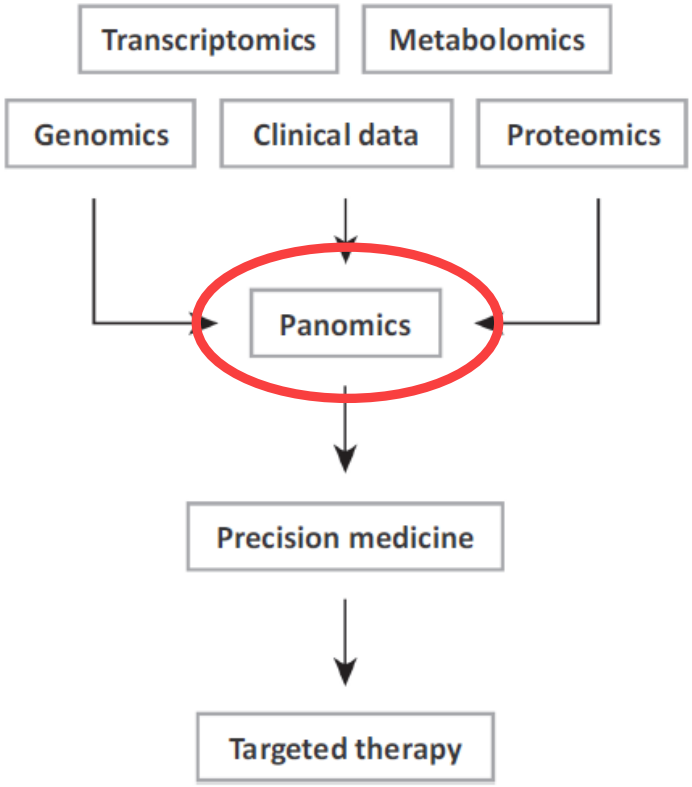
- ✓ *How to decipher complex traits: molecular dissection*
- ✓ *Interpretation of data and practical applications*

Deciphering complex traits: the omics

Holistic approaches allow addressing complex issues, e.g.

Mechanisms (pathogenesis) of disease

Precision medicine



Trends in Molecular Medicine

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Panomics for Precision M

Charanjit Sandhu,[1,*] Alia Qureshi,[2] and Andrew Emili[1]

Disease

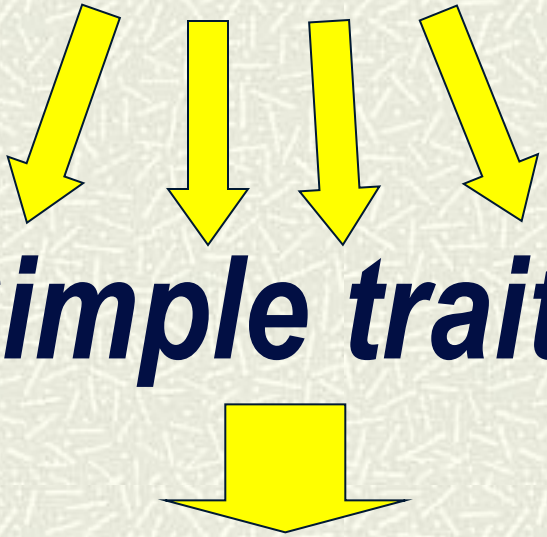
Reaction of an organism to pathogenic insults

Affected by the nature of the insults, environmental factors, current condition of the organism and its genetic make-up

Resolution of complex traits

PHENOTYPE

Complex traits



Simple traits

Structural, effector, signaling, regulatory proteins and pathways and their genes

Inheritance of complex traits

- Small additive effects of individual polymorphisms, mostly SNPs, composing the complex phenotype
- Gene-gene interactions identified by analysis of composed genotypes
- Genes/genotypes with major effects can be used as markers

Reminder: individual variability of the human genome

Single nucleotide polymorphisms (SNPs): 10 M throughout the genome

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

cgcgcggcctcctccttgtggtcatcctggtcctcctaaaccacctggac

Insertions/deletions (indels)

cgcgcggcctcctccttgtggccatcctggtcctcctaaaccacctggac

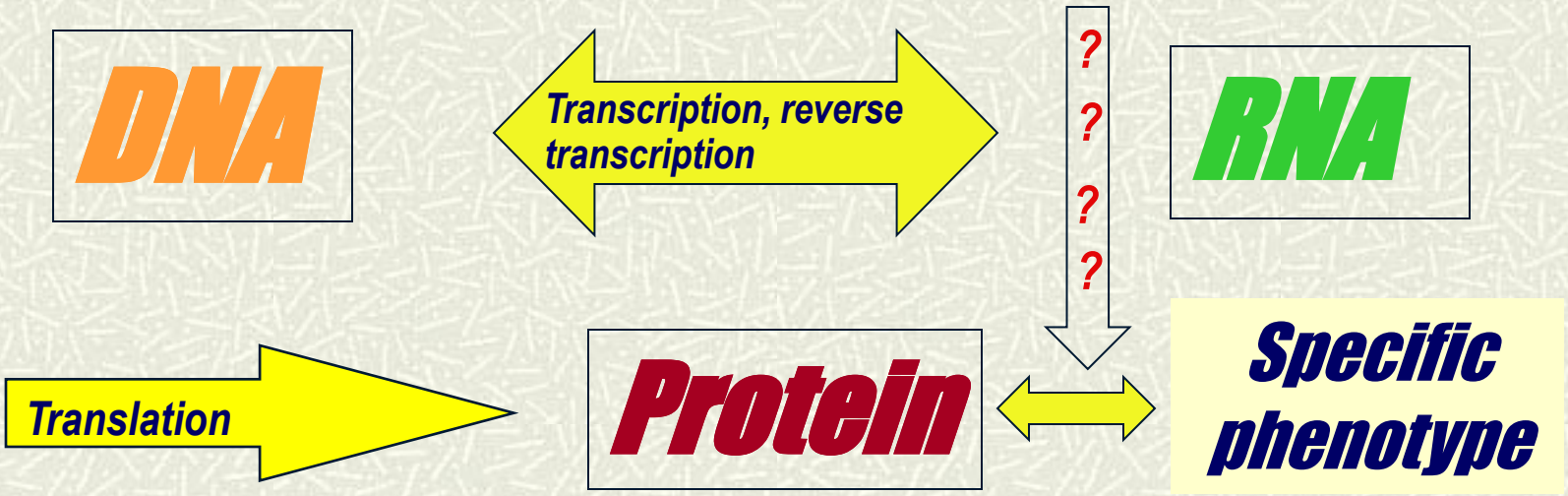
cgcgcggcctcctccttgtgg-------ctggtcctcctaaaccacctggac

Single nucleotide polymorphisms (SNP chips)

http://www.humgen.nl/SNP_databases.html

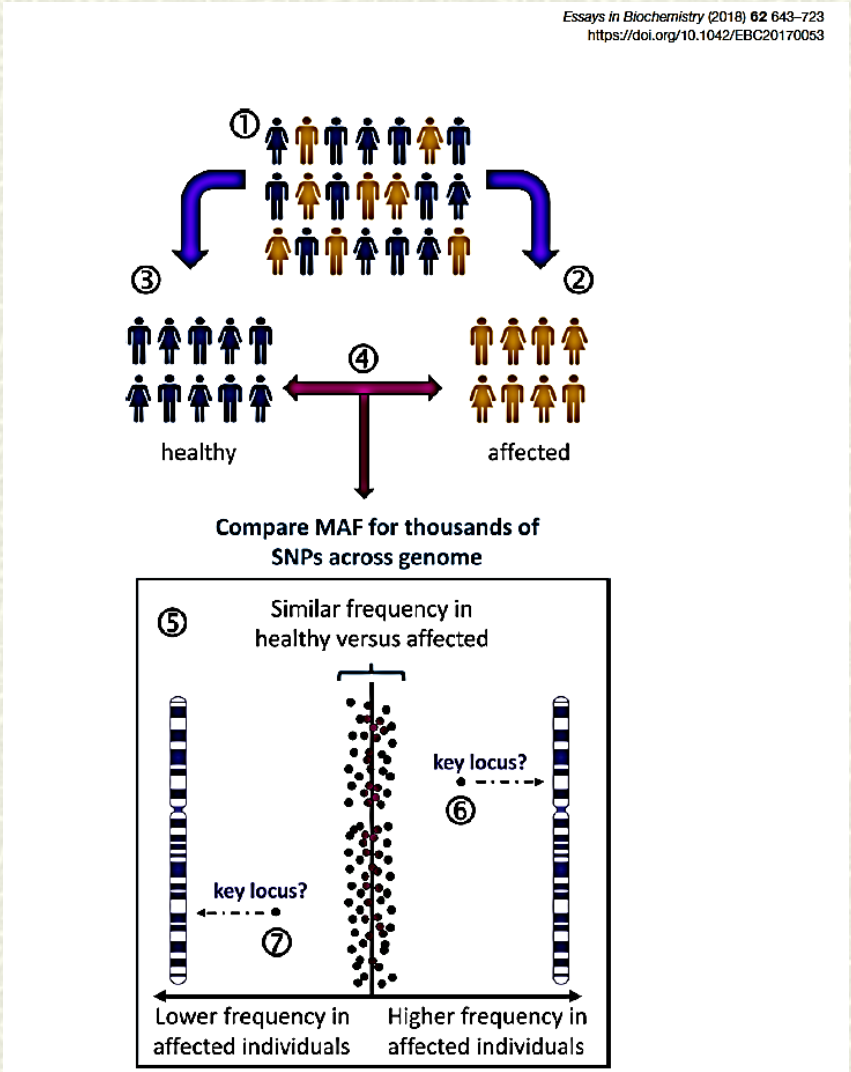
Decomposition of complex traits

Central dogma of molecular biology



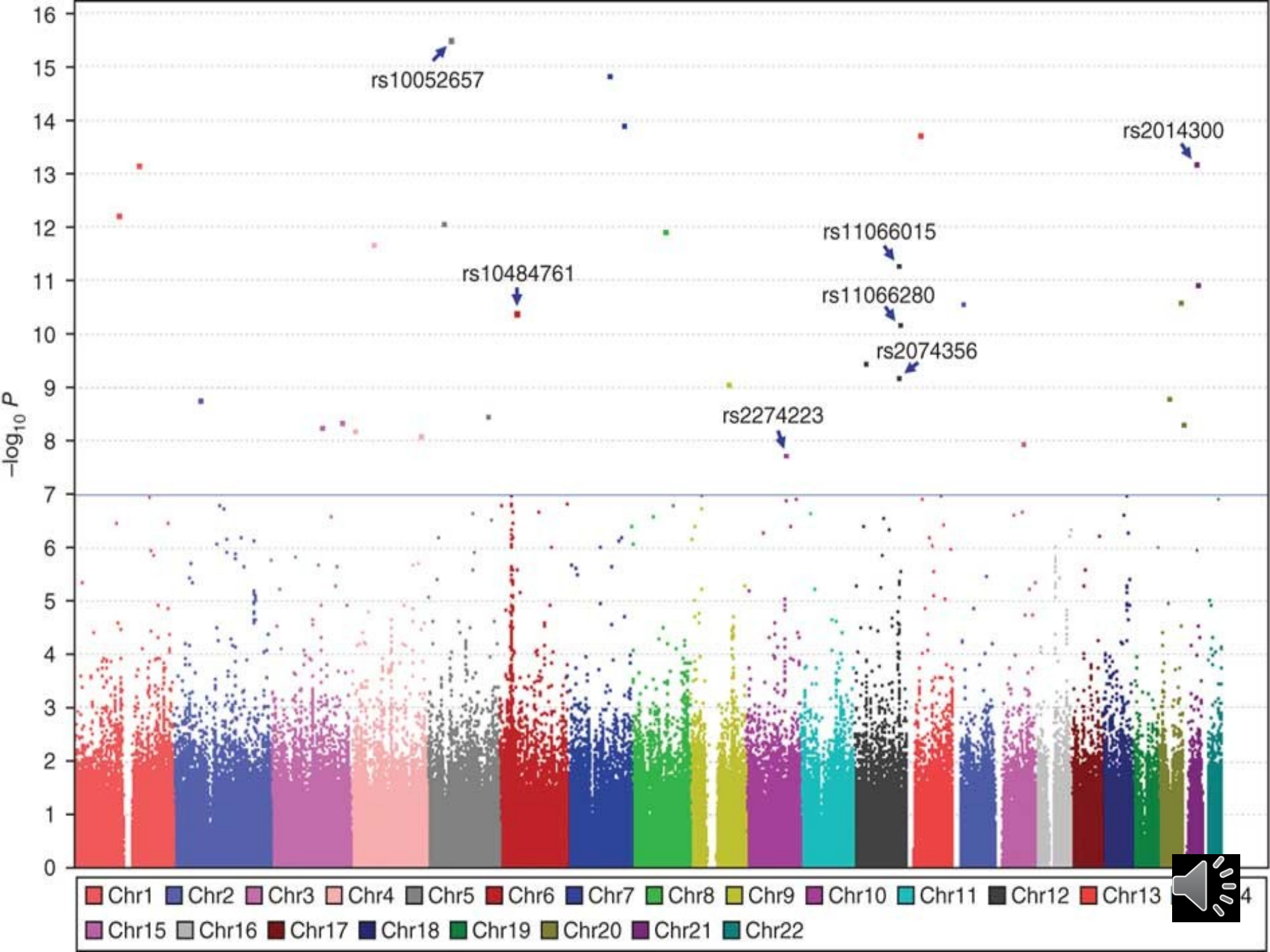
A tool:
Genome-wide association studies (GWAS)

Essays in Biochemistry (2018) **62** 643–723
https://doi.org/10.1042/EBC20170053



Principles of GWAS

- ✓ Genotyping of markers (SNPs) spanning the entire genome
- ✓ SNP chip: up to 1 Mb
- ✓ Statistical comparison of allele/genotype frequencies in groups with extreme phenotypes
- ✓ Identification of SNPs with major contribution to the phenotype studied


rs10052657
rs2014300
rs11066015
rs10484761
rs11066280
rs2074356
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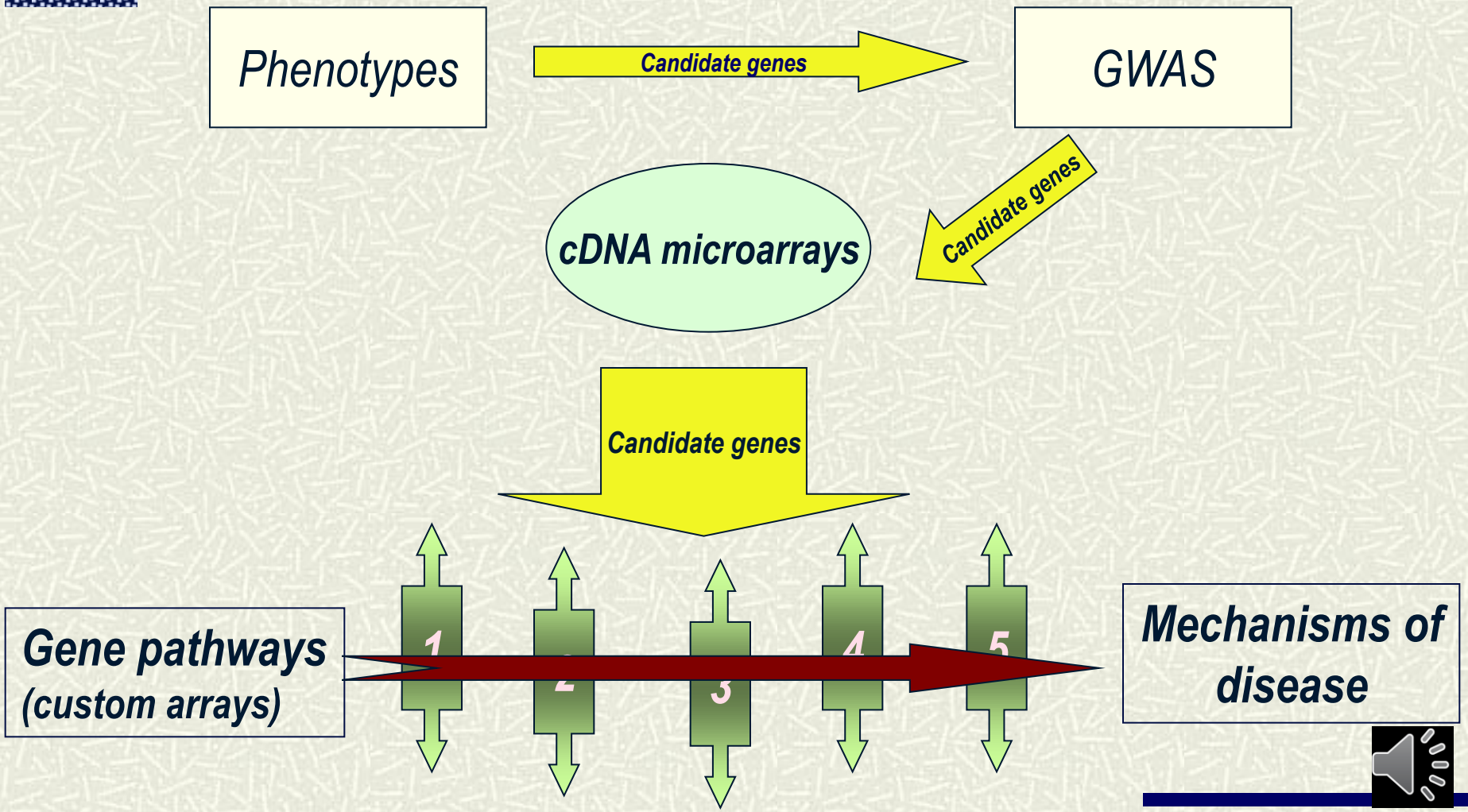
Chr1 Chr2 Chr3 Chr4 Chr5 Chr6 Chr7 Chr8 Chr9 Chr10 Chr11 Chr12 Chr13
Chr15 Chr16 Chr17 Chr18 Chr19 Chr20 Chr21 Chr22

Molecular dissection of complex traits



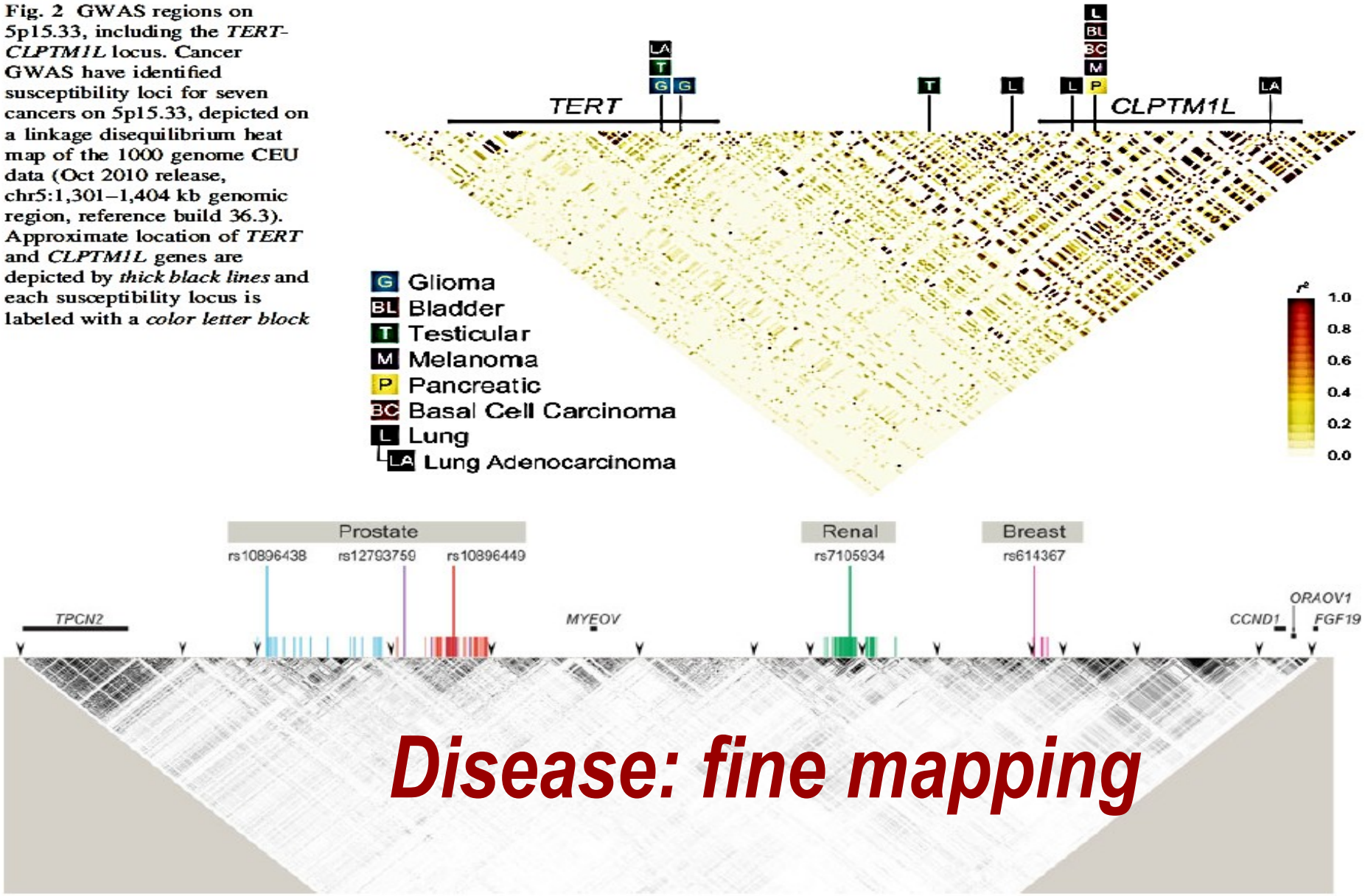


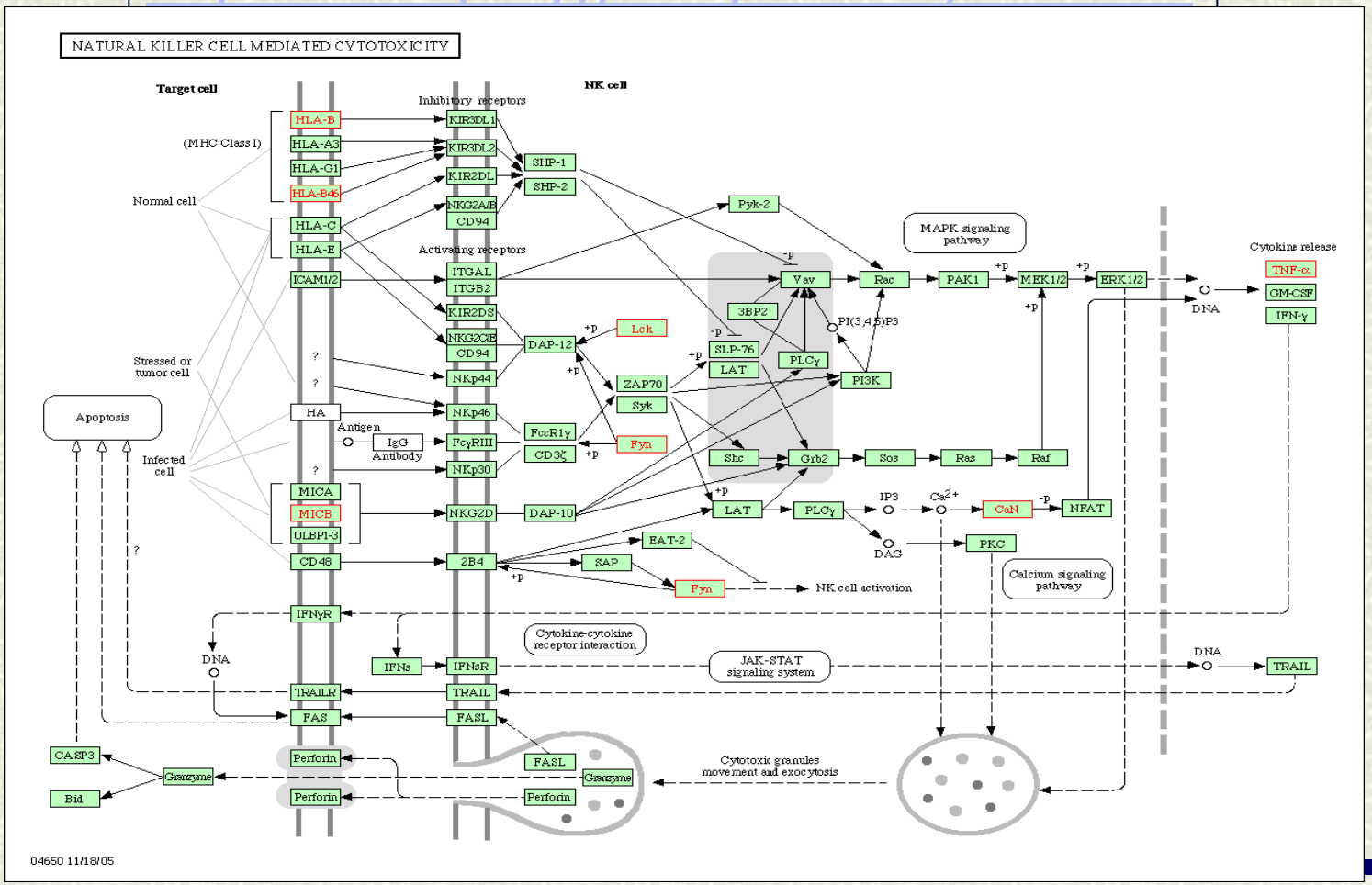
Fig. 2 GWAS regions on 5p15.33, including the *TERT-CLPTM1L* locus. Cancer GWAS have identified susceptibility loci for seven cancers on 5p15.33, depicted on a linkage disequilibrium heat map of the 1000 genome CEU data (Oct 2010 release, chr5:1,301–1,404 kb genomic region, reference build 36.3). Approximate location of *TERT* and *CLPTM1L* genes are depicted by *thick black lines* and each susceptibility locus is labeled with a *color letter block*

Fig. 3 Multiple-cancer susceptibility region on 11q13. Five susceptibility loci of three types of cancers—prostate, kidney, and breast localize to within less than 400 kb region on 11q13. The annotated surrogates ($r^2 > 0.8$) are superimposed on a linkage disequilibrium heat map of the 1000 genome CEU data (July 2010 release, chr11:68,564–69,233 kb genomic region, reference build 36.3). Reference genes (*black bar*), and recombination hotspots a g to HapMap (*black arrow heads*) found in the UCSC bro e annotated

Pathway analysis

(regulatory, signaling, metabolic pathways)

http://www.polygenicpathways.co.uk/



Example of a really complex disease: Genes associated with atherosclerosis/hypercholesterolemia and Alzheimer's disease

Family	Gene
Cholesterol and lipoprotein-related	A2M, ABCA1, APOA1, APOA4, APOC1, APOC2, APOC3, **APOE**, CD36, CETP, HMGCR, LDLR, LIPA, LRP1, LRP6, LPA, LPL, OLR1, SREBF1
Cytokines	CCL2, CCR2, IL1B, IL1RN, IL6,IL18, TGFB1, TNF
Oxidative stress	ALDH2, GSTM1, GSTT1, HFE, MPO, NOS3, PON1, PON2
Nuclear receptor and related	CYP19A1, ESR1, PPARA
Proteases	ACE, CST3, MMP1, MMP3, SERPINE1
Miscellaneous	BCHE, CBS, CD14, CRP, GNB3, HLA-A2, HTR6, ICAM1, MEF2A, MTHFR, PTGS2, TLR4

How to prioritize?

Pavlides *et al. Genome Medicine* (2016) 8:84
DOI 10.1186/s13073-016-0338-4

Genome Medicine

DATABASE Open Access

Predicting gene targets from integrative analyses of summary data from GWAS and eQTL studies for 28 human complex traits

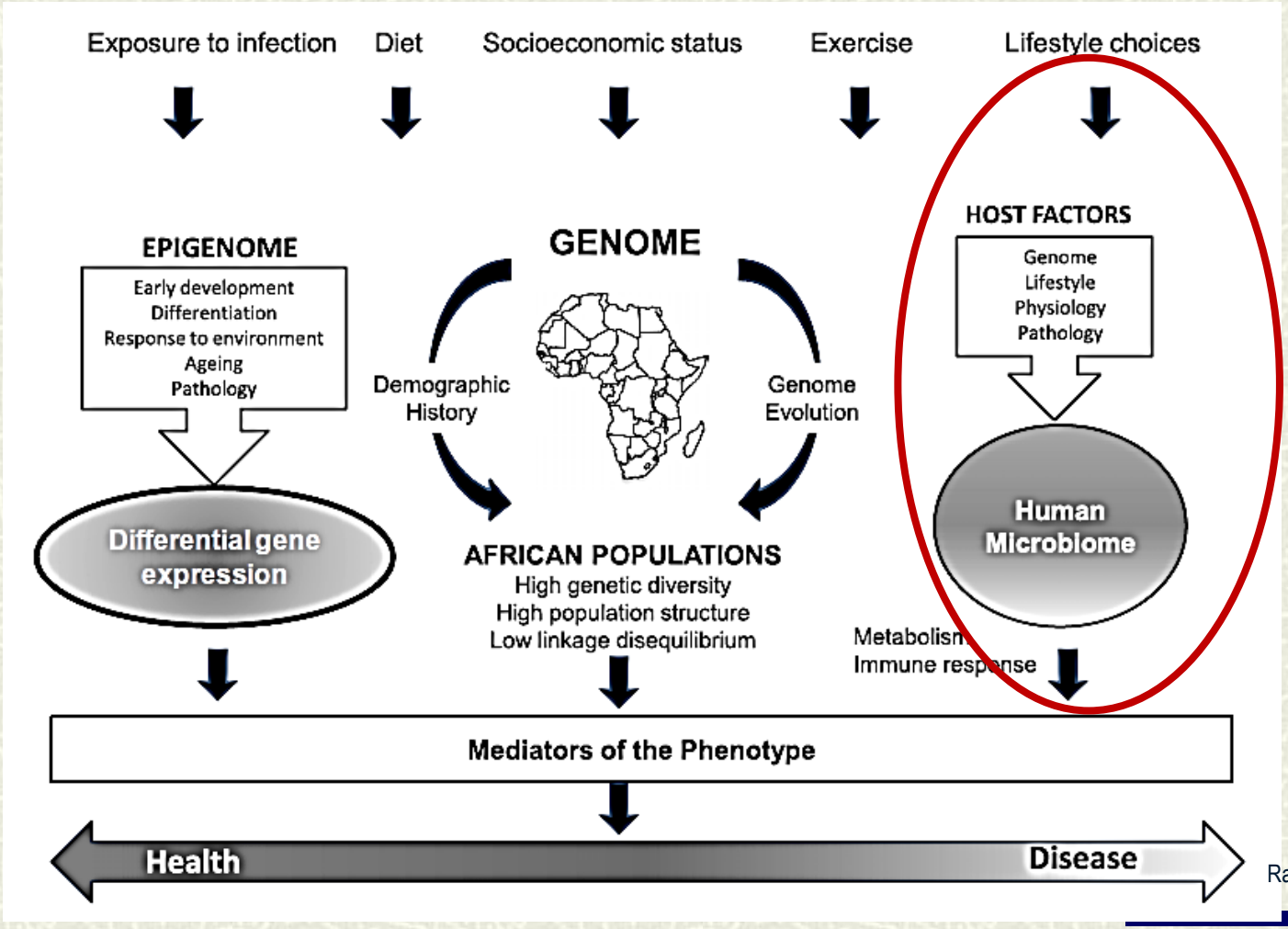
Jennifer M. Whitehead Pavlides†, Zhihong Zhu†, Jacob Gratten, Allan F. McRae, Naomi R. Wray and Jian Yang*

Abstract

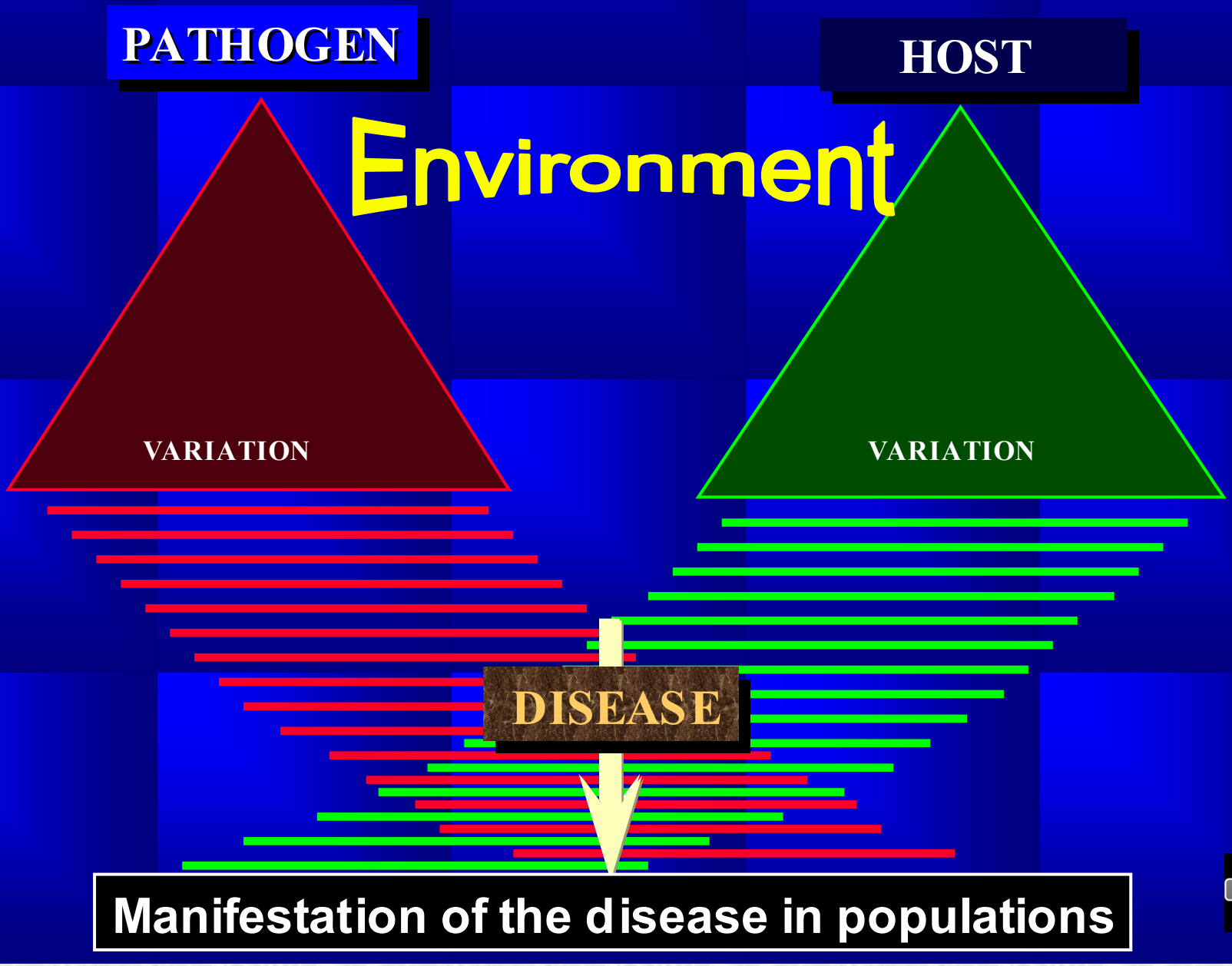
Genome-wide association studies (GWAS) have identified hundreds of genetic variants associated with complex traits and diseases. However, elucidating the causal genes underlying GWAS hits remains challenging. We applied the summary data-based Mendelian randomization (SMR) method to 28 GWAS summary datasets to identify genes whose expression levels were associated with traits and diseases due to pleiotropy or causality (the expression level of a gene and the trait are affected by the same causal variant at a locus). We identified 71 genes, of which 17 are novel associations (no GWAS hit within 1 Mb distance of the genes). We integrated all the results in an online database (http://www.cnsgenomics/shiny/SMRdb/), providing important resources to prioritize genes for further follow-up, for example in functional studies.

Keywords: Genome-wide association studies (GWAS), Expression quantitative trait loci (eQTL), Summary data-based Mendelian randomization (SMR), Complex traits

An example: genetic susceptibility to infections



Infectious disease



Genetic resistance and tolerance

as defined by Doeschl/Wilson & Kyriazakis (2012)

*Resistance: ability to reduce pathogen replication in the host

vs.

*Tolerance: ability to maintain homeostasis in the presence of replicating pathogen

Susceptibility	Tolerance, carrier status, shedding	Resistance

non-genetic factors, selection

* Difficult to uncoupling them
Different genes may be involved

Infectious disease as a result of host-pathogen interactions

„The infection must be seen in the context of the countermeasures produced by the parasite, and judged as a dynamic interaction of host and parasite rather than the clearance of an inert antigen by the host immune response“

Riffkin et al.,

Infectious disease as a result of host-pathogen interactions

- ✓ *Disease as a defense reaction of the host*
- ✓ *Often unique host/pathogen combinations*
- ✓ *Individual variability in using different immunological mechanisms against the same pathogen*
- ✓ *Symptomatologies determined mostly by the pathogens or by the host*

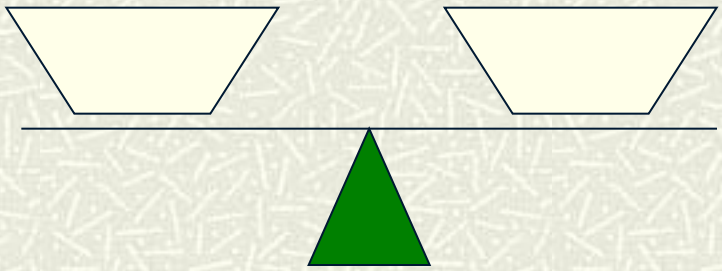
Scylla and Charybdis of immune responses: genetic variation

The dilemma:

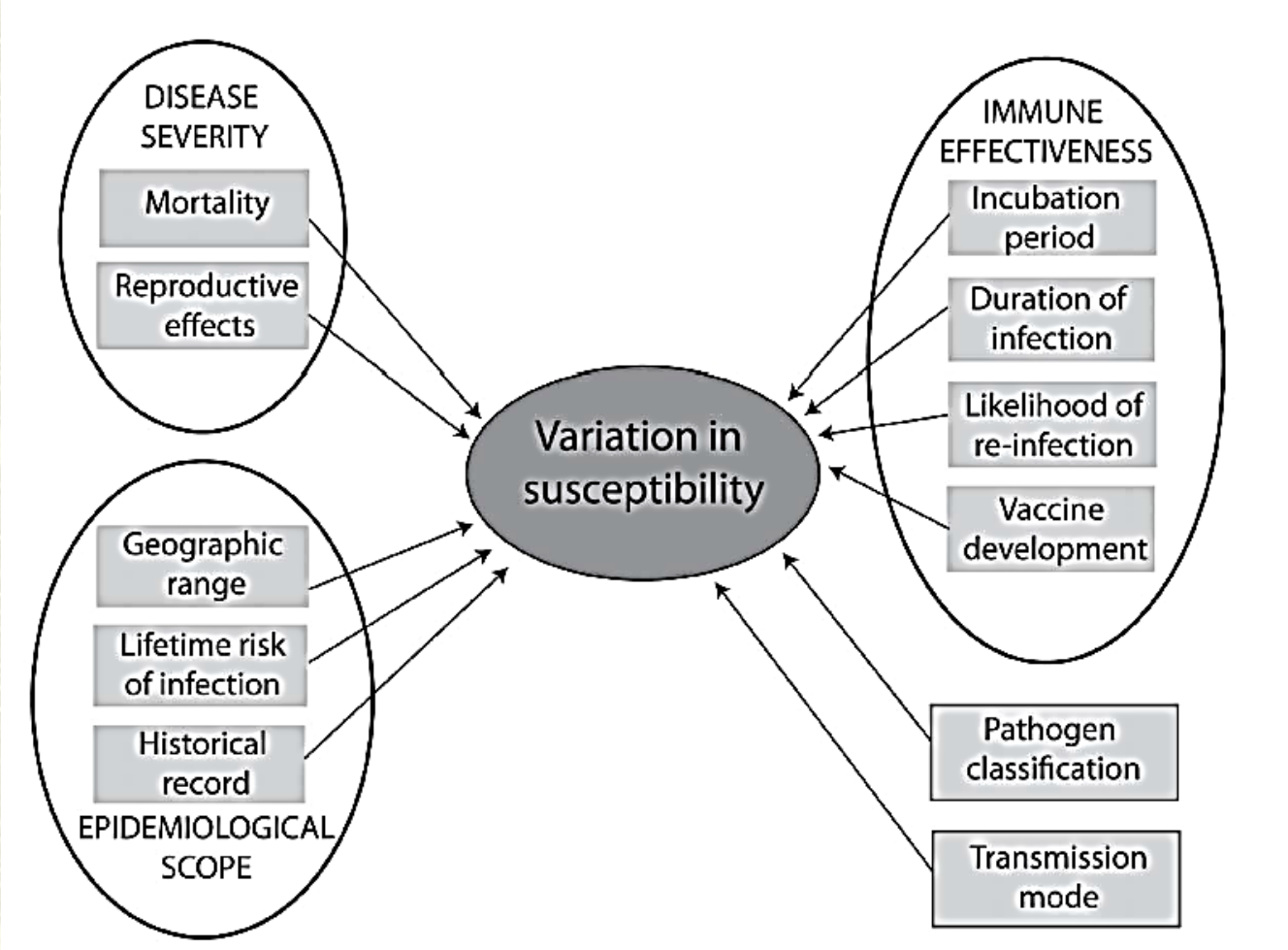
too high/too low immune responses?

Protective immunity
Resistance to infection

Autoimmunity
Inflammation



Genetic susceptibility to disease as a complex trait



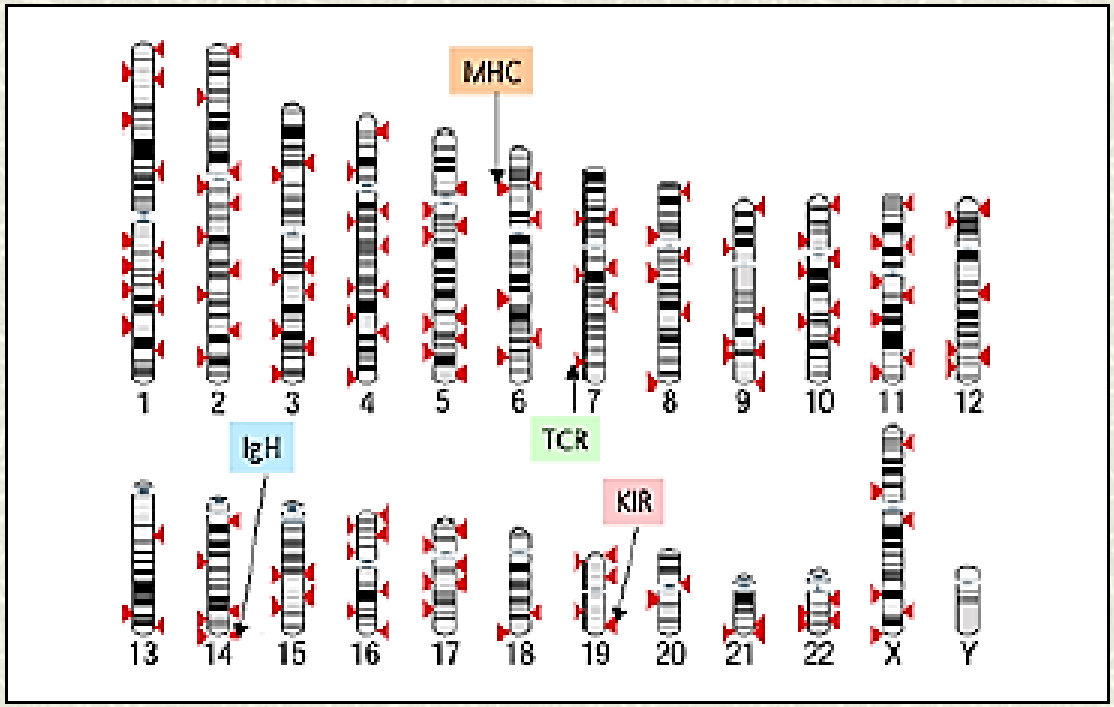
Baker, Antonovics 2012

Immunity-related (IR) genes: the immunogenome

- ✓ *Genes involved in host immune reactions*
- ✓ *Immunome: products of IR genes*
- ✓ *Despite the same biological importance, IR genes underlie many different functions in all branches of immunity*

Immunogenome and immunome

5% of the mammalian genome (~1,000 human genes) are protein coding genes related to immune mechanisms



Ortutay et al. Immunogenetic

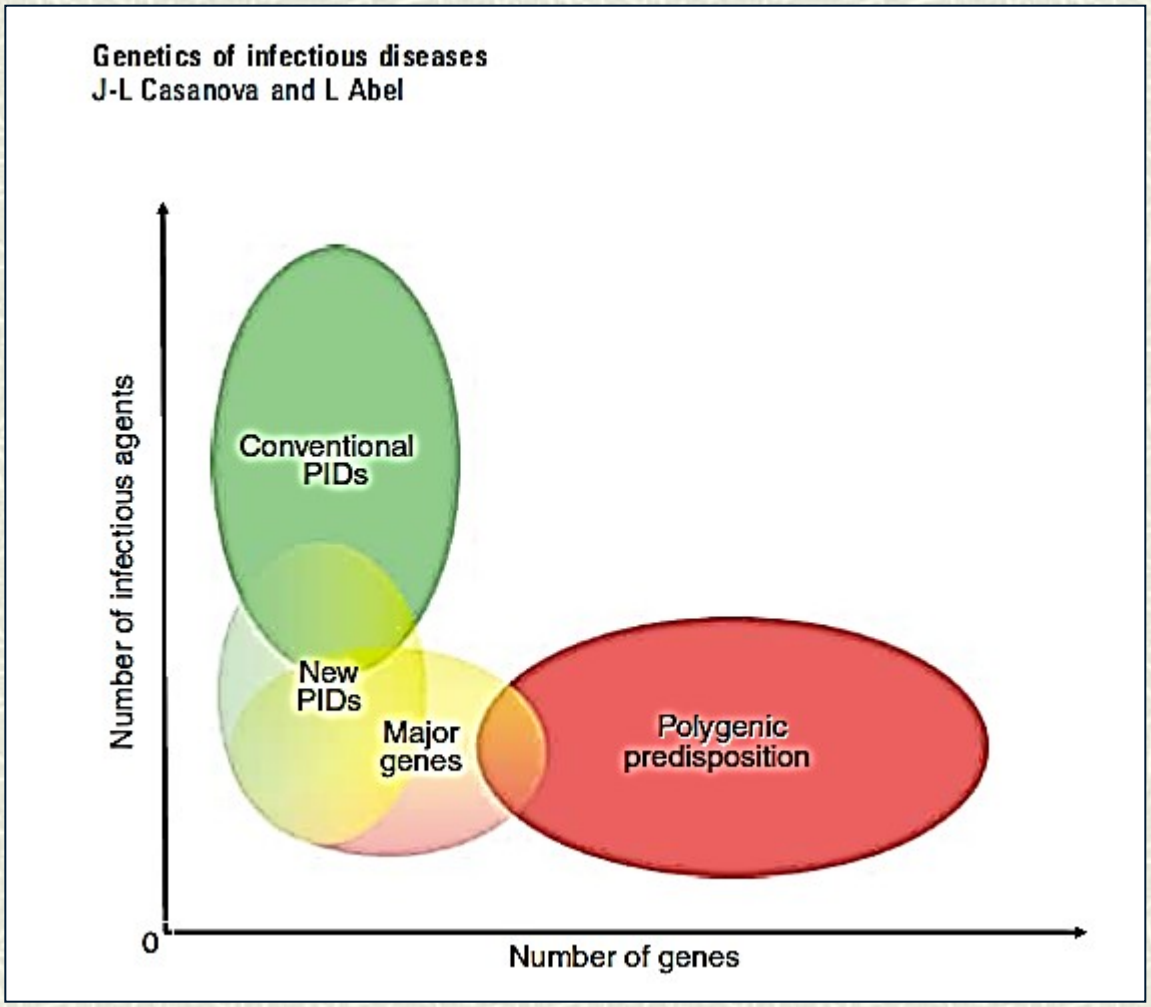
Immunity-related (IR) genes and disease

- ✓ *Immune functions as simple and/or complex traits (Mendelian vs. complex inheritance)*
- ✓ *Immune functions in mechanisms of infectious diseases*

Genetic resistance/susceptibility to infections

- ✓ Genes affecting health (interactions with environmental factors)
- ✓ Their polymorphisms are not causative for diseases, but they influence reactions of the host to environmental pathogens
- ✓ Pathogens as a driving force of evolution: IR genes/immunogenome have been shaped by evolutionary interactions with pathogens,
- ✓ In practical terms, resistance/susceptibility are usually relative to a population average

Genetic resistance/susceptibility to infections: modes of inheritance



Casanova, Abel EMBO J 2007

Mendelian inheritance

- Major effects
- Expected to result from low-frequency variants
- Less knowledge than for complex traits

Mendelian disorders of immunity to infection associated with predisposition or resistance to specific infections

Infectious agent	Clinical phenotype	Immunological phenotype	Gene
Neisseria	Invasive disease	MAC deficiency	*C5*, *C6*, *C7*, *C8A*, *C8B*, *C8G*, *C9*
	Invasive disease	Properdin deficiency	*PFC*
Mycobacteria	MSMD	IL-12/23–IFN-γ deficiency	*IFNGR1*, *IFNGR2*, *STAT1*, *NEMO*, *IL12B*, *IL12RB1*
	Disseminated tuberculosis		
Streptococcus pneumoniae	Invasive disease	IRAK-4 deficiency	*IRAK4*
Epstein-Barr virus	X-linked lymphoproliferative disease	SAP deficiency	*SH2D1A*
Human papillomavirus	Epidermodysplasia verruciformis	EVER1 or EVER2 deficiency	*EVER1*, *EVER2*
Plasmodium vivax	Natural resistance	Lack of receptor for pathogen	*DARC*
Human immunodeficiency virus-1	Natural resistance	Lack of receptor for pathogen	*CCR5*
Norovirus	Natural resistance	Lack of receptor for pathogen	*FUT2*

Picard et al Curr Opin Immunol 2006

GWAS and infections in humans

Table 1 Genetic loci identified by genome-wide association studies for host susceptibility to infectious diseases

Disease	Pathogen	Gene or locus	Biological mechanism
AIDS[1]	Human immunodeficiency virus-1	Major histocompatibility complex, class I (*HLA-B–HLA-C*), *CCR5*	Acquired immunity, deletion of viral co-receptor
Hepatitis B[2]	Hepatitis B virus (HBV)	Major histocompatibility complex, class II (*HLA-DP*)	Acquired immunity
Hepatitis C[3,4]	Hepatitis C virus (HCV)	*IL28B*	Innate immunity
Leprosy[5]	*Mycobacterium leprae*	Major histocompatibility complex, class II (*HLA-DR–DQ*), *NOD2*, *TNFSF15*, *RIPK2*, *CCDC122* and *C13orf31*)	Acquired and innate immunity, and unknown mechanisms
Tuberculosis[8]	*Mycobacterium tuberculosis*	18q11.2 (*GATA6*, *CTAGE1*, *RBBP8*, *CABLES1*)	Unknown
Meningococcal disease[7]	*Neisseria meningitidis*	*CFH*, *CFHR3*, *CFHR1*	Innate immunity

De Bakker, Telenti Nature Genet 2010

Genetic resistance/susceptibility to infections: untranslated genome

- ✓ *Most GWAS hits observed in (protein) non-coding regions*
- ✓ *Many SNPs found in regulatory regions of protein coding genes*
- ✓ *Effects on expression and consequently on diseases, including infections*

Genetic resistance/susceptibility to infections: untranslated genome

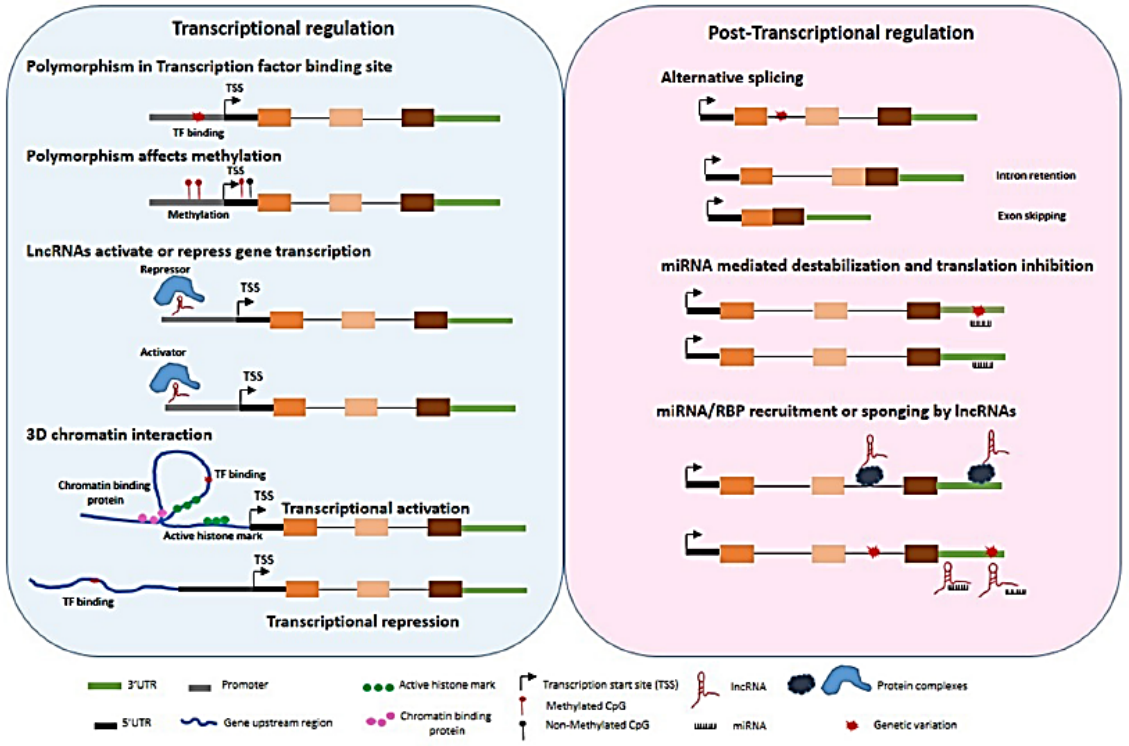


FIGURE 1 | Untranslated gene variations influence regulation of gene expression. Disease associated polymorphisms may alter methylation, transcription factor binding in the gene promoter regions, recruitment of repressor or activators, 3 dimensional chromatin structure, splicing, miRNA binding to 3′UTR, transcriptional and post-transcriptional regulation of target genes through variation in lncRNA expression and function.

Mechanisms of immunity-related diseases studied with genomic tools

- ✓ Infections
- ✓ Allergies
- ✓ Autoimmunity
- ✓ Complex immunopathologies

Examples of genetic susceptibility to infections

- ✓Norovirus, rotavirus (*FUT2)*
- ✓AIDS (CCR5)
- ✓Malaria (Duffy)
- ✓*COVID 19 (AB0, IFN type 1)*

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INVITED REVIEW

Immunological Reviews WILEY

The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity

Inna G. Ovsyannikova | Iana H. Haralambieva | Stephen N. Crooke | Gregory A. Poland | Richard B. Kennedy

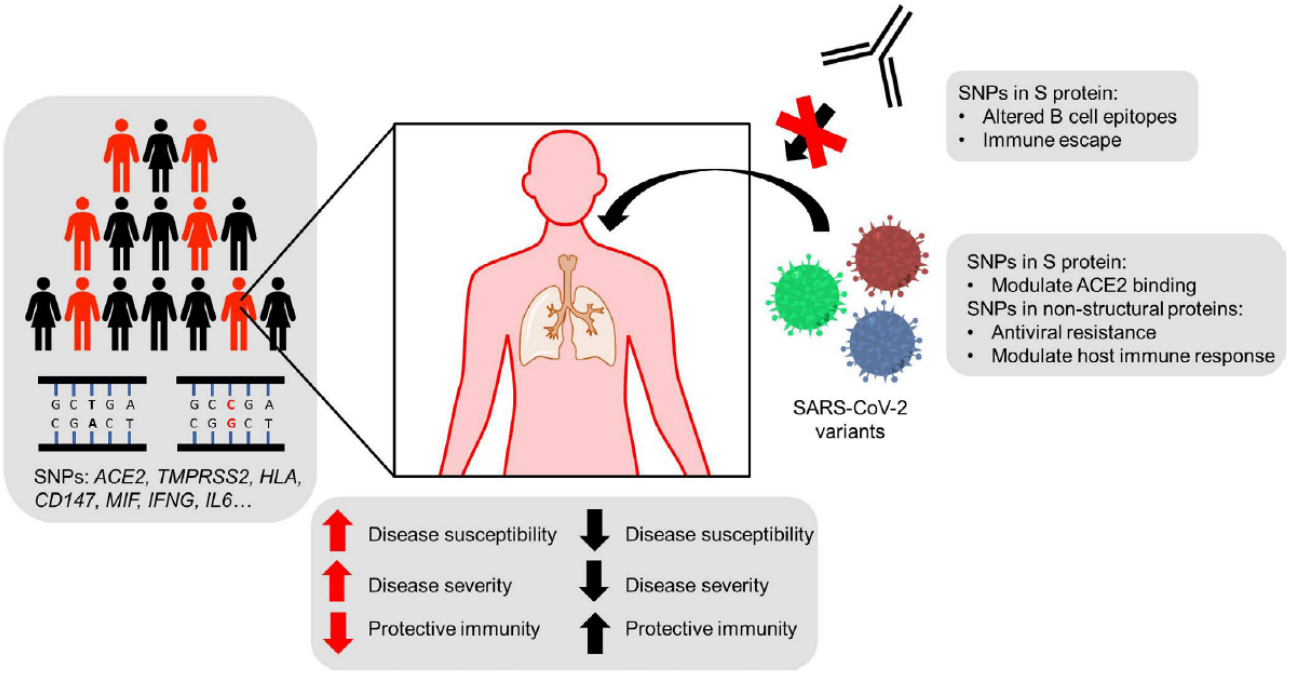
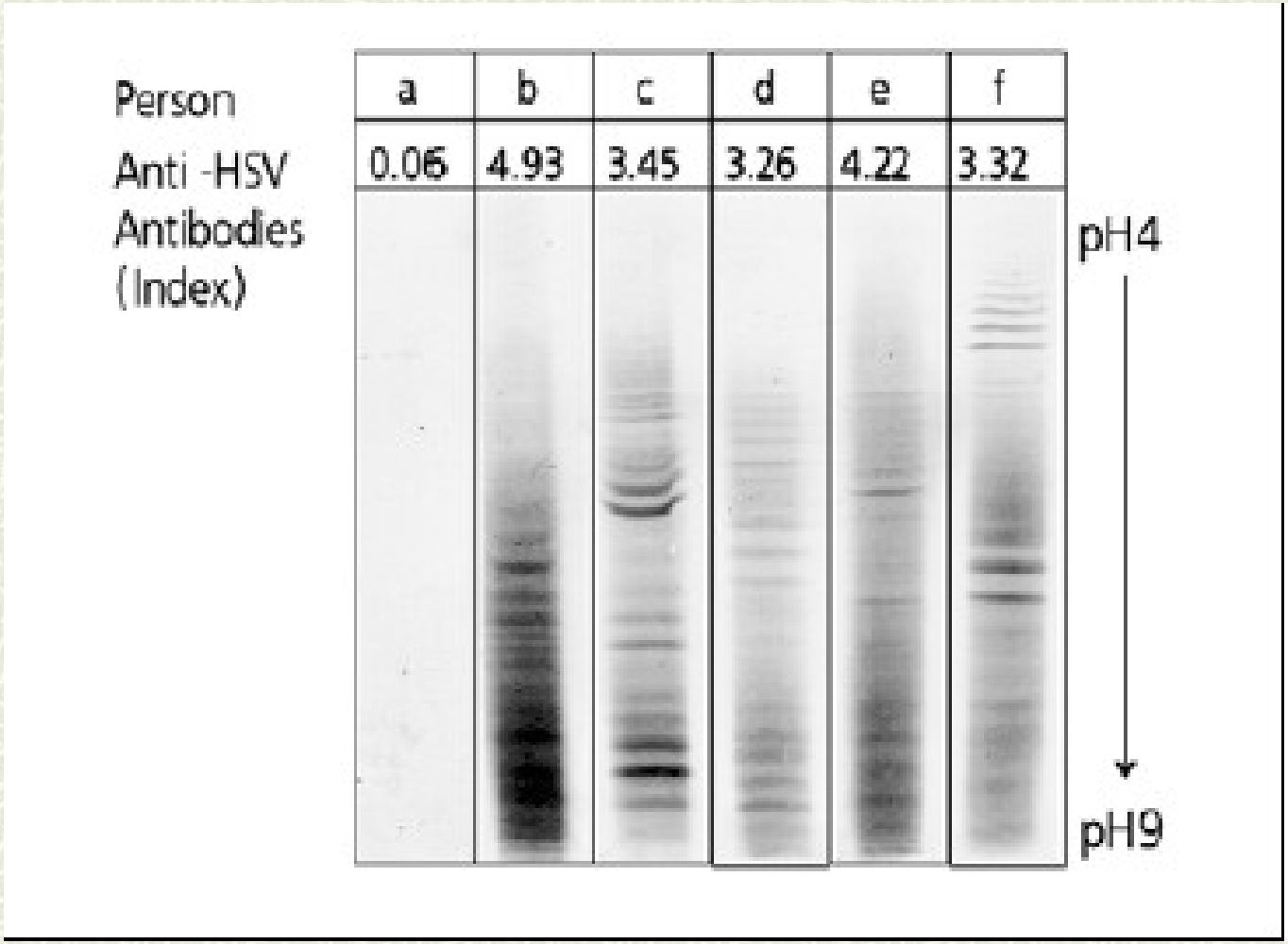


FIGURE 1 The impact of host genetics and viral variation on SARS-CoV-2 infection and COVID-19 severity. Individuals in the population harbor single nucleotide polymorphisms (SNPs) across a variety of genes (eg, *ACE2*, *TMPRSS2*, *HLA*, *CD147*, *MIF*, *IFNG*, *IL6*) that have been implicated in the pathology and immunology of SARS-CoV-2 and other pathogenic coronaviruses. These and other genetic variants may modulate disease susceptibility, increase or decrease disease severity, alter the variety of symptoms developed, and affect the magnitude and/or quality of the immune responses against SARS-CoV-2. In addition to host genetic variation, genetic variants of SARS-CoV-2 (and other pathogenic coronaviruses) can exhibit differences in biological activity. Single amino acid mutations in the spike glycoprotein can modulate ACE2 binding or alter B cell epitopes to promote immune escape or render monoclonal antibodies ineffective, while mutations in non-structural/accessory proteins can promote the development of resistance to antivirals, alter T cell epitopes, disrupt cell mediated immunity, and modulate host cellular interactions with viral particles

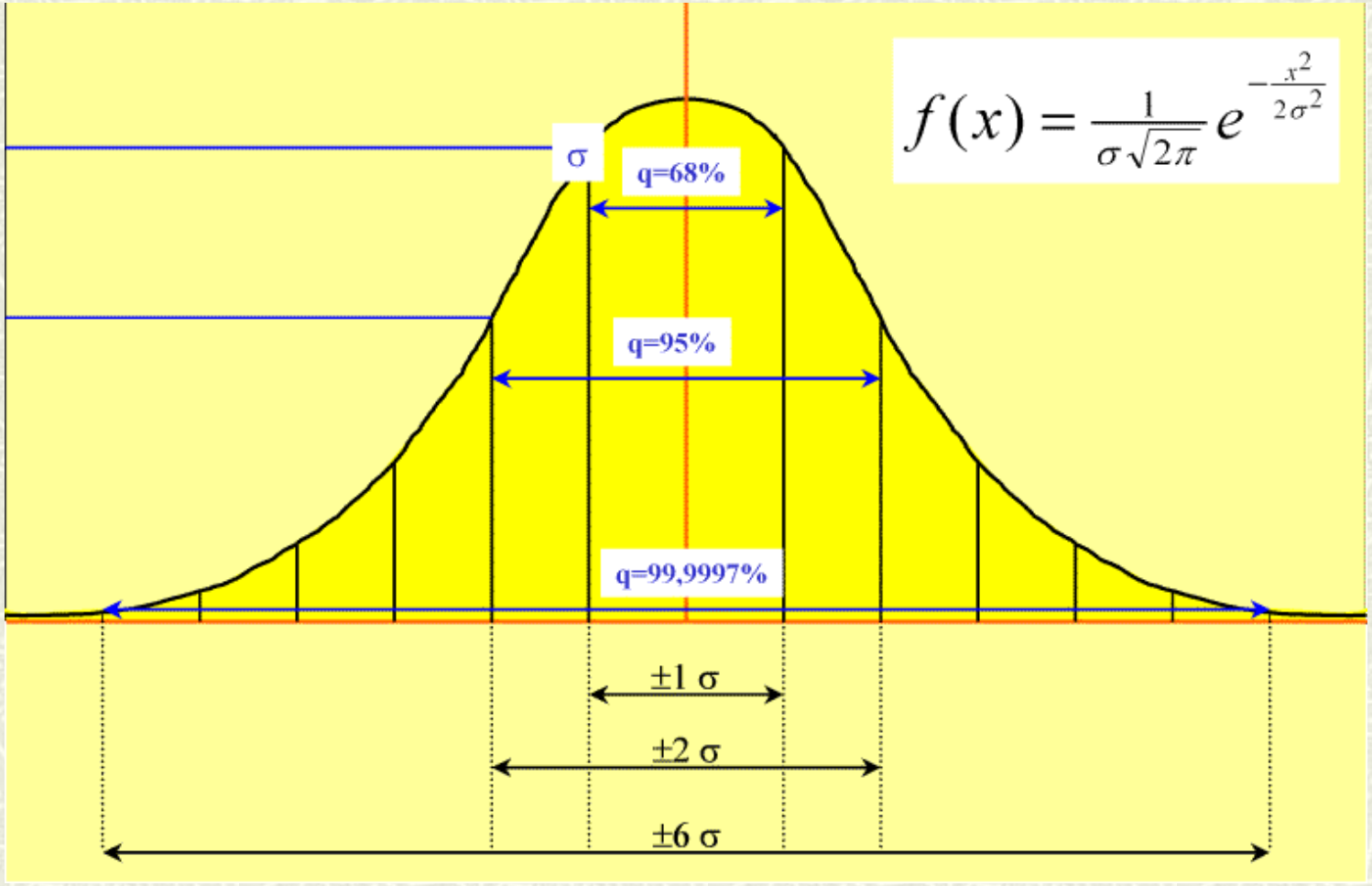
Individual variation in antibody responses



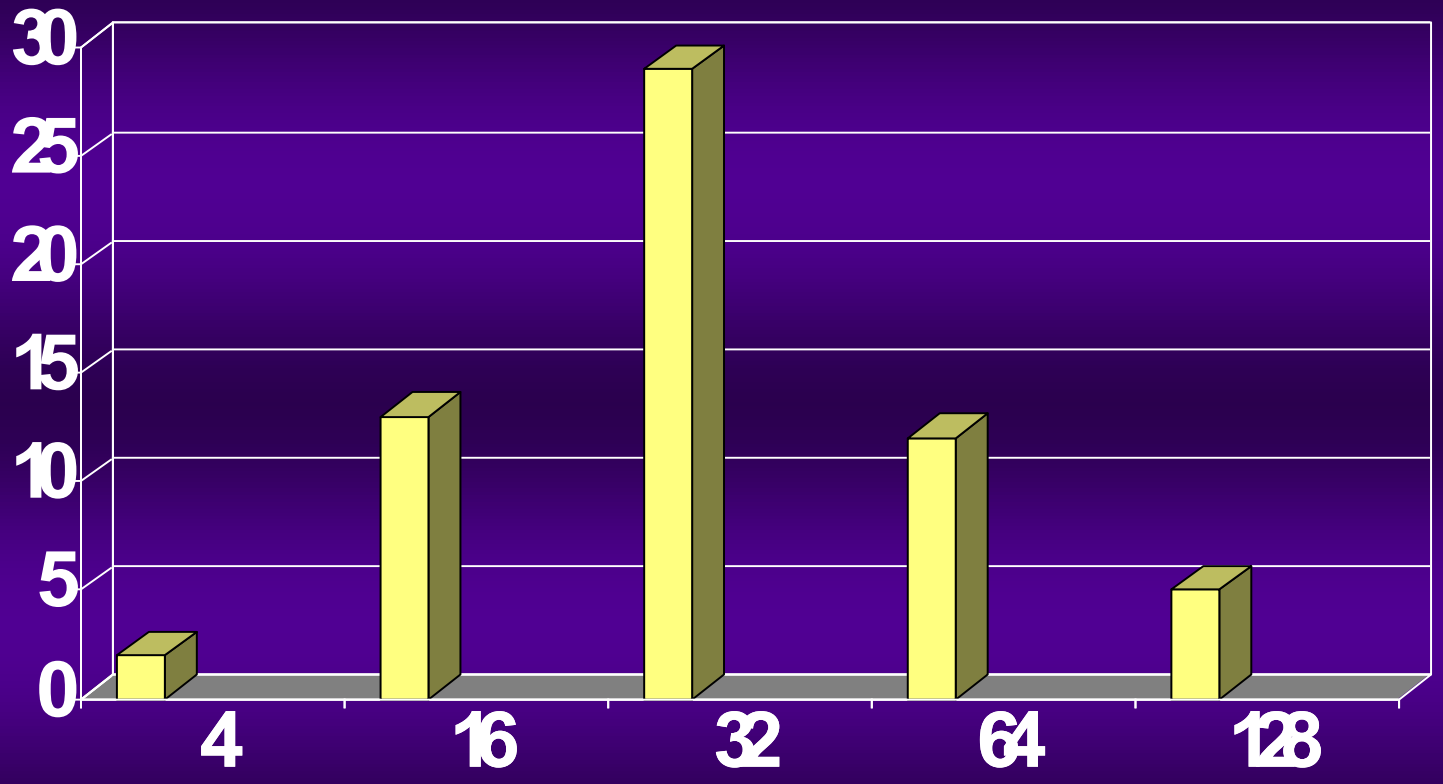
Genetics of vaccination

- ✓ *Individual variation in post-vaccination IRs*
- ✓ *Pharmacogenomics*

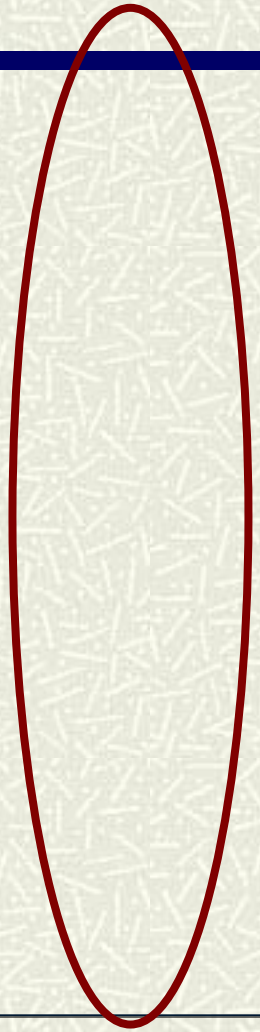
Normal (Gaussian) distribution



Titers of post-vaccination antibodies in a real experiment (N=61)



Genetics of vaccination



Genetic susceptibility to disease as a complex trait

Leading Edge

Essay

Cell

Infectogenomics: Insights from the Host Genome into Infectious Diseases

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DOI 10.1016/j.cell.2006.02.003

Five years into the human postgenomic era, we are gaining considerable knowledge about host-pathogen interactions through host genomes. This "infectogenomics" approach should yield further insights into both diagnostic and therapeutic advances, as well as normal cellular function.

Cell *124*, February 24, 2006 ©2006 Elsevier In

Genetics of infectious disease in humans

(Quintana-Murci et al. Nature Immunology 8, 2007: 1165-1171

- **Clinical:** definition of genes and alleles responsible for individual susceptibility to infection: > 200 *PIDs*
- **Epidemiological:** definition of genes and alleles responsible individual susceptibility to infection, *GWAS*
- **Evolutionary:** study of genes selected by previous infections: *evolution/speciation, signatures of selection (interspecies/within species), population diversity*

Evolutionary aspects

http://ancients-bg.com/wp-content/uploads/2016/04/0021.jpg

- ✓ *Migrations and sympatry of hominoid populations, sharing different infections*
- ✓ *Lower overall genome diversity and mostly lower IR gene in Neanderthals*
- ✓ *Higher MHC gene diversity*
- ✓ *Archaic Neanderthal haplotypes TLR6-TLR1-TLR10*
- ✓ *Susceptibility to COVID 19, ethnic differences*

Ethical issues: how to cope with information generated by genomic techniques

Examples

- ✓ Mendelian diseases:

e.g. carrier tests, PGD

- ✓ Complex diseases

e.g. interpretation of GWAS, DTC

Only people understanding principles can cope with this problem

Practical applications

Minimum variant for you

- ✓ *To know, when and where to refer a patient for a genetic consultation*
- ✓ *To know how to interpret clinical geneticist's reports*
- ✓ *To know when not to refer a patient for a genetic consultation*