AFTER THE HUMAN GENOME PROJECT: APPLYING GENOMICS TO HEALTH

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Rare Diseases and Orphan Drugs
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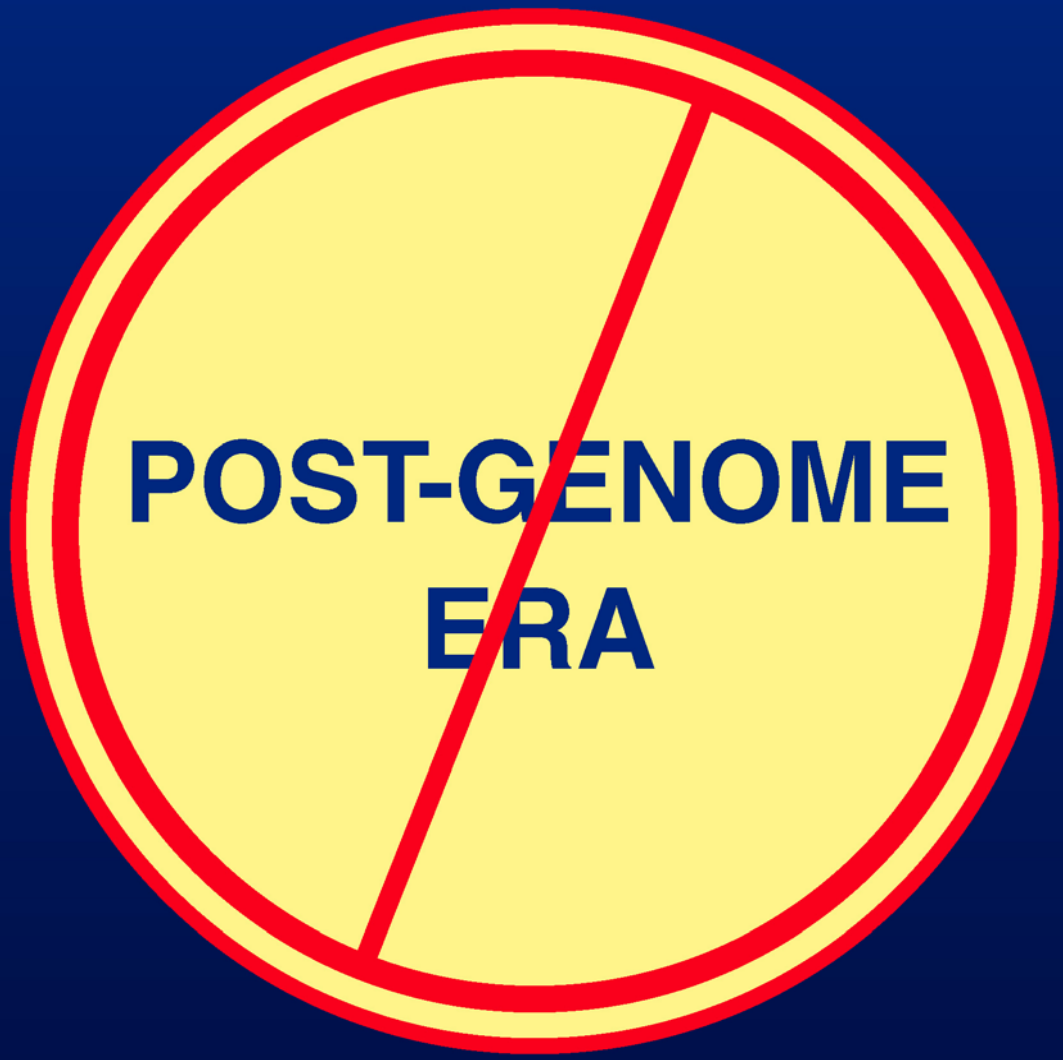


WELCOME TO THE GENOME ERA

New Approaches to Understanding Rare Disease Etiology

- Now that we have more tools to do so, should we reorient our thinking from:

  Phenotype → Biological Causation

- To:

  Biological Causation → Phenotype

New Approaches to Understanding Rare Disease Etiology

Hypomorphic mutations in syndromic encephalocele genes are associated with Bardet-Biedl syndrome

Carmen C Leitch[1], Norann A Zaghloul[1], Erica E Davis[1], Corinne Stoetzel[2], Anna Diaz-Font[3], Suzanne Rix[3], Majid Al-Fadhel[4], Richard Alan Lewis[5], Wafaa Eyaid[4], Eyal Banin[6], Helene Dollfus[2], Philip L Beales[3], Jose L Badano[1,7] & Nicholas Katsanis[1]

Meckel-Gruber syndrome (MKS) is a genetically heterogeneous, neonatally lethal malformation and the most common form of syndromic neural tube defect (NTD). To date, several MKS-associated genes have been identified whose protein products affect ciliary function[1–5]. Here we show that mutations in *MKS1*, *MKS3* and *CEP290* (also known as *NPHP6*) either can cause Bardet-Biedl syndrome (BBS) or may have a potential epistatic effect on mutations in known BBS-associated loci. Five of six families with both *MKS1* and *BBS* mutations manifested seizures, a feature that is not a typical component of either syndrome. Functional studies in zebrafish showed that *mks1* is necessary for gastrulation movements and that it interacts genetically with known *bbs* genes. Similarly, we found two families with missense or splice mutations in *MKS3*, in one of which the affected individual also bears a homozygous nonsense mutation in *CEP290* that is likely to truncate the C terminus of the protein. These data extend the genetic stratification of ciliopathies and suggest that BBS and MKS, although distinct clinically, are allelic forms of the same molecular spectrum.

defects that include failure of the neural tube to close in mice and perturbed gastrulation movements in zebrafish[14,15]. Although NTDs are infrequent in *Bbs*$^{-/-}$ mice and have never been reported in individuals with BBS, they are the cardinal manifestation of another ciliopathy, MKS, a syndrome of encephalocele, cystic kidneys, hepatic fibrosis and polydactyly. MKS has been attributed to ciliary dysfunction, because of (i) the presence of disease-causing mutations in four genes[1,3–5,16], each of which is present in ciliary proteomic collections[17], and (ii) the localization of all MKS-causing proteins to the basal body, primary cilium or both[2,3,18–20].

Mutations in at least three BBS genes cause MKS-like phenotypes but not encephalocele[21]. These observations, together with the presence of encephalocele in our *Bbs4* mutant mice[14], prompted us to hypothesize that MKS might represent a more severe variant of BBS. If true, mutations in *bona fide* MKS genes should contribute causal and/or modifying mutations to BBS. To test this hypothesis, we first sequenced the coding exons of both *MKS1* isoforms (see Methods for accession numbers; **Supplementary Fig.** 1 online) in 155 BBS-affected families, without preselection for mutational load in the known BBS loci. We identified potentially pathogenic mutations in six families, in

Nature Genetics; April 2008:443-448

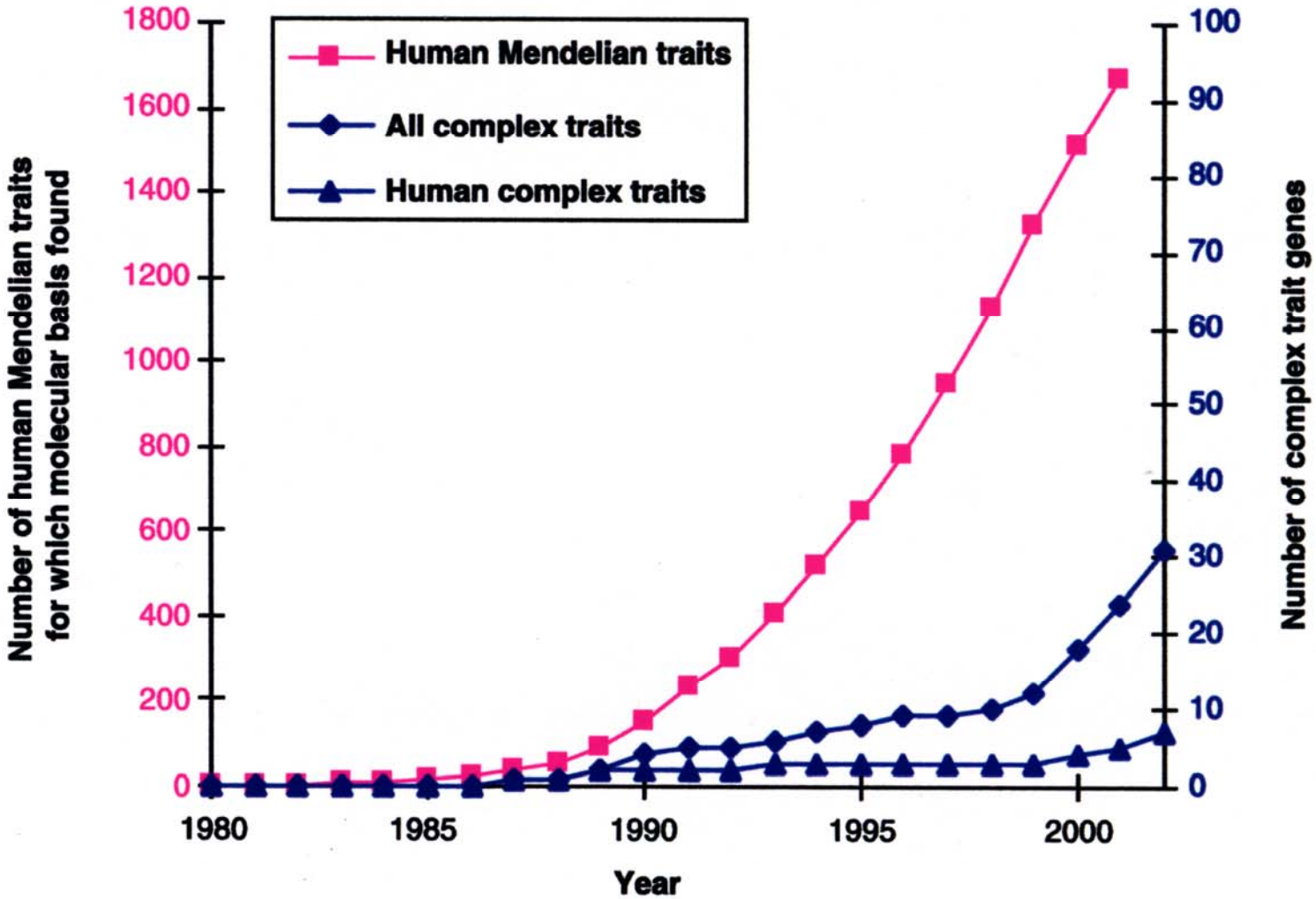
New Approaches to Understanding Etiology

- ENCODE

  (*ENC*yclopedia *O*f *D*NA *E*lements)
  - There is more to the genome than our exons, and thus more mechanisms for genetic misadventure – e.g., copy number variation, epigenetic phenomena
  - We likely still have not fully catalogued these mechanisms, let alone searched for their roles in causing rare diseases

New Approaches to Understanding Etiology

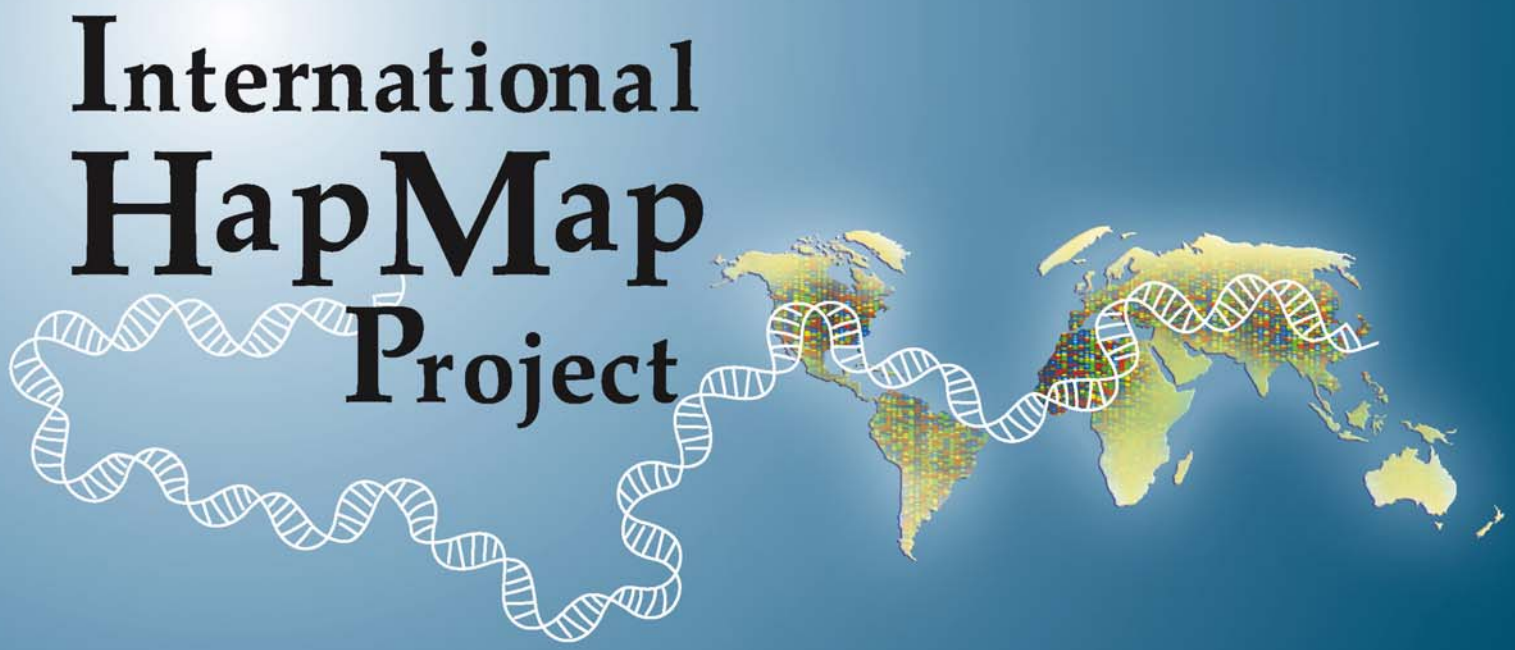
- Might genome-wide association studies (GWAS) be of any help?
  - Allow an "agnostic" approach to etiology
  - Used, so far, in common diseases; but, could similar approaches help discover
    - Etiology of rare diseases, if sufficient well-phenotyped cases are amassed by research networks?
    - Modifier genes for "single gene" (is there really such a thing?) disorders?



Glazier et al., Science 298:2345-9, 2002

Whole Genome Association Approach to Common Disease: The 2002 View

- Identify all 10 million common SNPs
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to 20 billion genotypes
- At 50 cents a genotype, that's **$10 billion** for each disease



www.hapmap.org

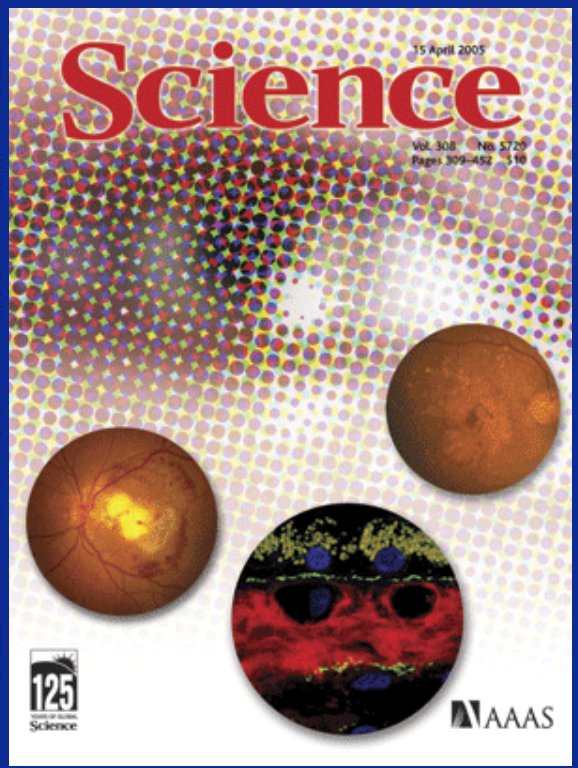
Whole Genome Association Approach to Common Disease: The 2007 View (The HapMap Era)

- Identify optimum set of ~500,000 (or more) variants
- Collect 1000 cases and 1000 controls
- Genotype all DNAs for all SNPs
- That adds up to ~~20~~ **1** billion genotypes
- And, a genotype now costs ~~50 cents~~ 1/12 of a penny, so that's about ~~$10 billion~~ **$800,000** for each disease

An Early Result from the HapMap: Age-Related Macular Degeneration

Complement Factor H Polymorphism in Age-Related Macular Degeneration

Robert J. Klein,[1] Caroline Zeiss,[2*] Emily Y. Chew,[3*] Jen-Yue Tsai,[4*] Richard S. Sackler,[1] Chad Haynes,[1] Alice K. Henning,[5] John Paul SanGiovanni,[3] Shrikant M. Mane,[6] Susan T. Mayne,[7] Michael B. Bracken,[7] Frederick L. Ferris,[3] Jurg Ott,[1] Colin Barnstable,[2] Josephine Hoh[7†]

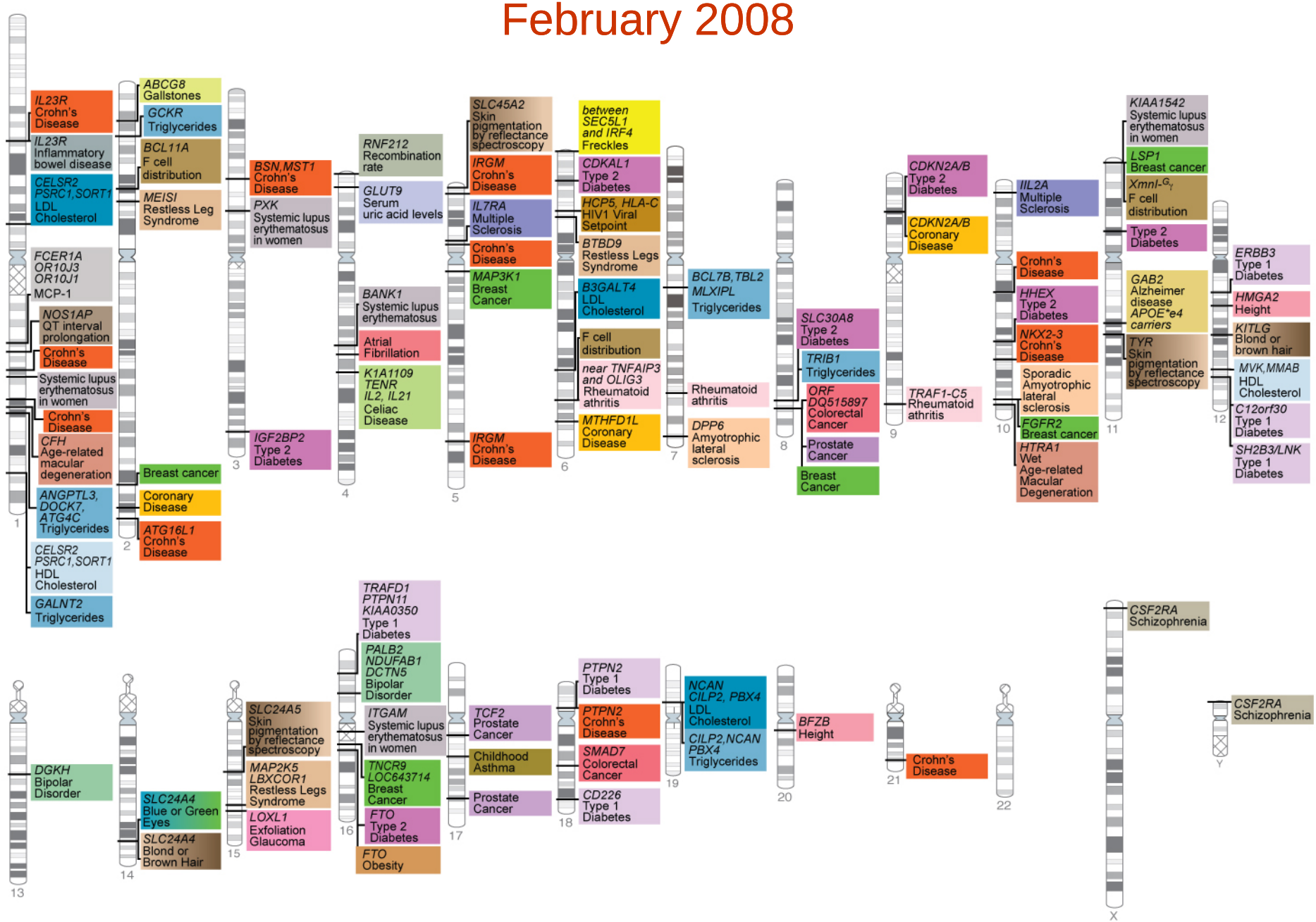


Science 2005; 308:385-9

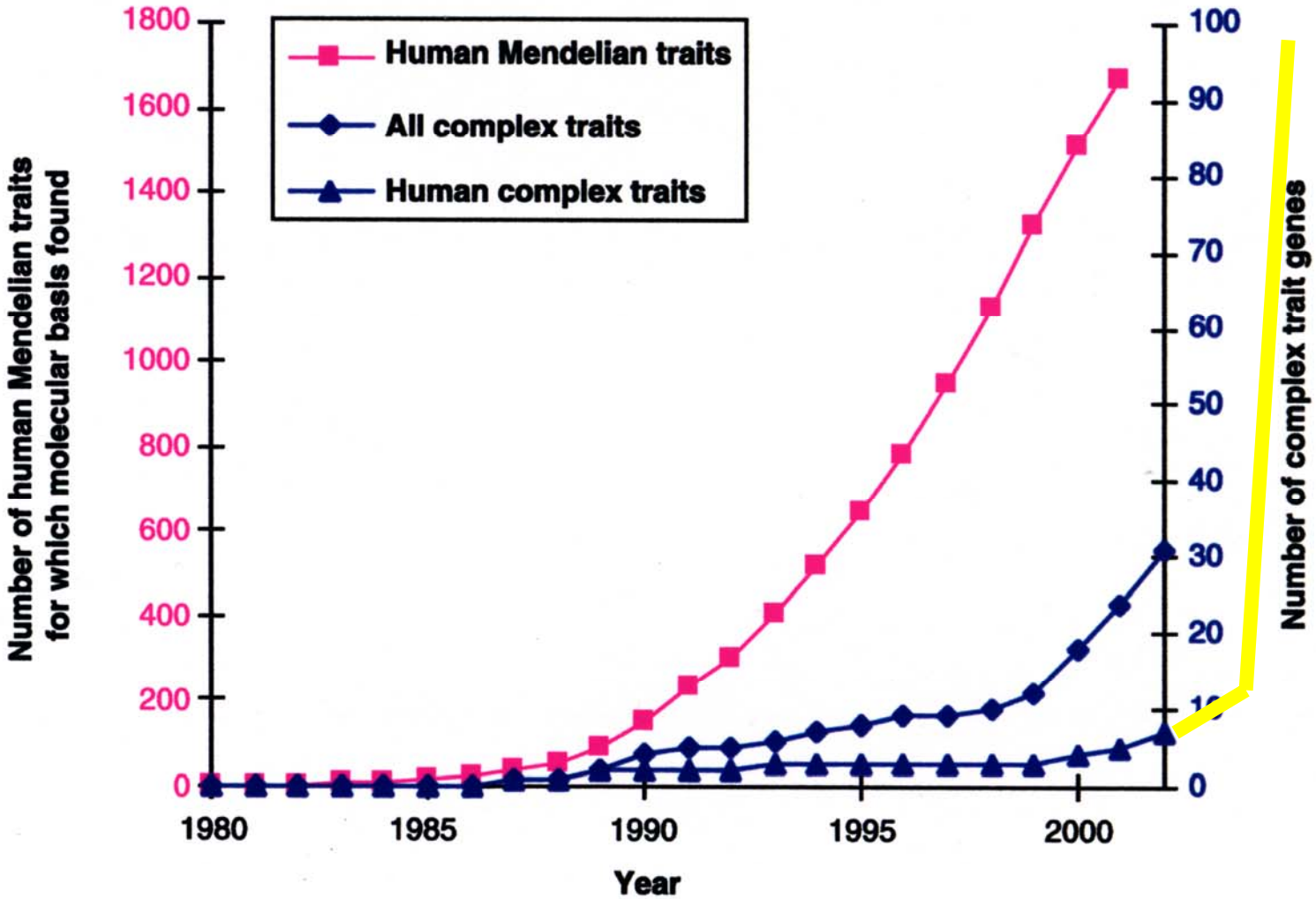
Using the same strategy, another major risk locus was identified (HTRA1).

Together these account for ~50% of risk, suggest AMD may be an inflammatory disease, and point to new approaches to prevention and treatment.

February 2008



Manolio, Brooks, Collins, J. Clin. Invest.; 2008



Glazier et al., Science 298:2345-9, 2002

New Approaches to Understanding Etiology

- E.g., use of large-scale sequencing capability to do such things as:
  - Aid researchers who have mapped Mendelian disorders to intervals of ≤ ~10 Mb
  - Resequence each exon on the X-chromosome of individuals with any of the >100 mapped, but uncloned, X-linked human diseases
  - Analysis of DNA samples from rare recessive or new dominant lethal disorders

New Approaches to Diagnosis

- Not truly new; e.g., array CGH
- Next stop: high-throughput genotyping and sequencing
- What happens when the entire genome of a newborn with question of a rare disease can be fully sequenced for less than the cost of one day's hospital stay …

New Approaches to Therapeutics

- Might genomic tools and approaches help find therapies for rare, single-gene disorders, making stories like that of losartan in Marfan syndrome much more common?

Among Them All, How Many Human Genes Do Current Drugs Target?

- ~500 (2.5% of the genome)
- ~1,000 (5%)
- ~5,000 (25%)
- ~10,000 (50%)
- ~ 15,000 (75%)
- ~20,000 (100%)

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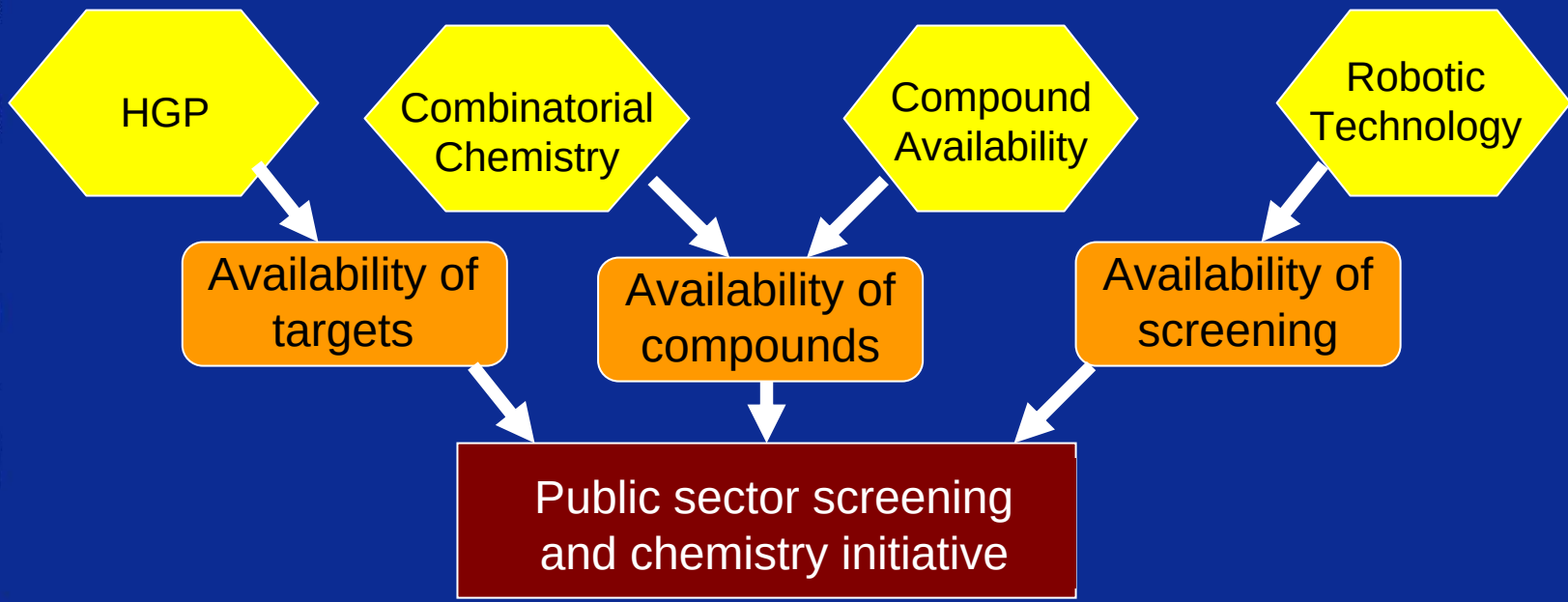
Recent Developments in Biology and Chemistry Enable "Chemical Genomics"



Chemical Genomics

- Offers academic researchers access to small organic molecules for use as chemical probes to study cellular pathways in greater depth
- Will help validate new targets for drug therapy more rapidly, and enable researchers in the public and private sectors to take these targets and compounds and move them through the drug-development pipeline

The Future Is Now…NCGC and the Molecular Libraries Network

NIH Dives Into Drug Discovery

10 Oct 2003
Vol. 302 Science

NIH unveils an ambitious plan to create molecular libraries as a first step to finding potential new drugs. But is it feasible?

Why would Elias Zerhouni want to quiz me about drug discovery? wondered Merck neurogeneticist Chris Austin after getting a

search. Then again, if NIH can convince drug companies to pick up where academic science leaves off, the eventual wind-

NEWS OF THE WEEK

MOLECULAR BIOLOGY

NIH Gears Up for Chemical Genomics

18 June 2004
Vol. 304 Science

The National Institutes of Health (NIH) announced last week that it is creating an industrial-scale high-tech screening center. It will be the hub of an academic consortium that will create a library of molecules to probe cells and search for new drugs. But one difficult issue—how to divvy up intellectual property rights—is not yet resolved.

The planned molecular library is part of NIH Director Elias Zerhouni's road map, a set of initiatives announced last September whose $2.2 billion, 6-year budget is funded by contributions from NIH's

Speed demon. This Kalypsys machine, which can screen more than 1 million small molecules per day for activity in different cell and protein assays, will sit in NIH's new Chemical Genomics Center.

says will be freely available to the community. Researchers could ask to patent a find in special cases, Austin notes. But at a recent meeting, some university tech-transfer officers strongly objected to restrictions on patenting, suggesting that researchers should be allowed to obtain property rights but not enforce them for academic use. Some scientists see both sides: "I'm all for open exchange," says biochemist Laura Kiessling of the University of Wisconsin, Madison, but for certain discoveries, a patent could be "almost better … so somebody will manufacture" the product so more researchers can work with it.

NIH expects to announce a patent policy before an August

The Future Is Now

April 2008
Nature Medicine

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nature medicine

Identification of oxadiazoles as new drug leads for the control of schistosomiasis

Ahmed A Sayed[1], Anton Simeonov[2], Craig J Thomas[2], James Inglese[2], Christopher P Austin[2] & David L Williams[1]

Treatment for schistosomiasis, which is responsible for more than 280,000 deaths annually, depends almost exclusively on praziquantel. Millions of people are treated annually with praziquantel, and drug-resistant parasites thus are likely to evolve. Phosphinic amides and oxadiazole 2-oxides, identified from a quantitative high-throughput screen, were shown to inhibit a parasite enzyme, thioredoxin glutathione reductase (TGR), with activities in the low micromolar to low nanomolar range. Incubation of parasites with these compounds led to rapid inhibition of TGR activity and parasite death. The activity of the oxadiazole 2-oxides was associated with a donation of nitric oxide. Treatment of schistosome-infected mice with 4-phenyl-1,2,5-oxadiazole-3-carbonitrile-2-oxide led to marked reductions in worm burdens from treatments against multiple parasite stages and egg-associated pathologies. The compound was active against the three major schistosome species infecting humans. These protective effects exceed benchmark activity criteria set by the World Health Organization for lead compound development for schistosomiasis.

Schistosomiasis is a chronic disease caused by trematode flatworms of the genus *Schistosoma*. The disease remains a major, neglected, poverty-related health problem in many tropical areas[1]. The health burden resulting from schistosomiasis is estimated to include more

single drug for the treatment of schistosomiasis is not sustainable, and thus there is an urgent need to identify new targets and drugs for schistosomiasis treatment.

Schistosome parasites have a complex life cycle involving snail

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The Future Is Now

- NCGC is currently working with Forbes (Denny) Porter at NICHD on an assay for Smith-Lemli-Opitz syndrome, to identify compounds that act as protein chaperones for *DHCR7*, mutated in SLO.

New Research Collaborations

- Researchers can take advantage of new genomic tools/approaches to understand and treat rare and orphan diseases.
- This will usually occur most effectively and expeditiously if researchers are acutely aware of progress in genomics and/or cultivate working relationships with those savvy about such tools.