

Advances in understanding disease mechanisms, diagnosis and treatment using genetics and genomics

Richard P. Lifton, M.D., Ph.D.

Chair, Department of Genetics

Yale University School of Medicine

Understanding of disease causation is central to advancing prevention and effective therapy

- Infectious disease
 - Drain the swamp
 - Engineer hygiene
 - Vaccinate to prevent common infections
 - Develop therapy to treat specific pathogens

Basic science advances led to human genetics and genomics

- 1865: Individuals inherit one allele of each gene from each parent
- 1910: Genes are carried in a linear array on chromosomes
- 1944: DNA is the genetic material
- 1953: Structure of DNA suggests mechanism of replication
- 1960: Elucidation of genetic code
- 2001: Entire sequence of 3.1 B base pair human genome identifies the 'parts list' of humans

Examples in our lifetimes in which new understanding of pathogenesis has improved health outcomes

- Lowering LDL by inhibiting HMGCoA reductase reduces cardiovascular morbidity and mortality
- Imatinib (Gleevec) is an inhibitor of the Abelson tyrosine kinase that is required in ~95% of patients with chronic myelogenous leukemia
- Identification of HIV-1 as the cause of AIDS has led to development of simple diagnostic tests and new medications that have dramatically impacted the spread and course of disease
 - Reverse transcriptase inhibitors
 - Protease inhibitors
 - Integrase inhibitors

Study designs in genetics/genomics

- Mendelian traits
- Acquired (somatic) mutations in cancer
- Common variant associations in cases/controls
- Measuring gene expression differences in cases/controls
- Re-sequencing the genome

Impact of genetics/genomics on pathogenesis

- Alzheimer's disease
 - Rare mutations in amyloid precursor protein and gamma secretase
 - Common variants in ApoE
- Inherited and acquired mutations in cancer
 - BRCA1 and 2
 - IDH-1 in glioblastoma multiforme
- Blood pressure
 - Rare and common variants that alter renal salt handling change blood pressure
- Preeclampsia
 - Increased placental expression of sFlt

Impact on understanding ethnic disparities in disease prevalence

- Common variants in MYH9 markedly increase risk of kidney failure in African Americans with hypertension or HIV
- Common variants in PLPLA3 markedly increase risk of non-alcohol related fatty liver disease in Hispanic Americans

Path from gene identification to therapy

- From gene discovery need to understand steps that connect to health and disease
 - Need robust scientific enterprise with diverse expertise
- Identify ways to counteract effects of disease pathways or enhance health-promoting pathways
 - Need ‘broadband’ interactions between academia and industry with appropriate management of COI
- Need robust clinical trials to define best practices
- Need better delivery systems to ensure the public derives maximal benefit

Future of personalized medicine

- Two alternative visions:
 - We will treat each patient with drugs targeted to their specific and individualized abnormalities: great if differences among patients are large (e.g., CML)
 - We will understand common disease pathways in detail and target key rate-limiting steps, using the same targets in all/most patients: great if there are key targets/pathways common to all (e.g. salt and blood pressure)