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

PRESIDENT • CARSON FAMILY PROFESSOR, LABORATORY OF HUMAN GENETICS AND GENOMICS

The pathogenesis of most human diseases, and the consequence of mutation of 80 percent of human genes, is unknown. By developing and implementing robust exome sequencing, Lifton has provided evidence that loss of nearly every gene will have large effect on the risk of specific traits. These findings expand the scope of human genetics, provide insight into pathophysiology, and define new targets for risk determination, prevention, and therapy.

The prevention and treatment of human disease rests upon understanding disease mechanisms. Despite extensive efforts, the pathogenesis of most diseases remains poorly understood. Genomic approaches provide a means to establish causal relationships between genotypes and phenotypes by enabling the determination of the mechanisms that link them and identifying new targets for prevention, treatment, and diagnosis. The Mendelian era identified the consequence of mutation of only 3,000 of the 20,000 human genes. The conservation of human genes among vertebrates suggests the vast majority of the remainder will have large effects when mutated.

To explore this possibility, Lifton developed rapid and inexpensive exome sequencing and new analytic approaches, enabling large-scale discovery of rare mutations with large effects on human traits. His lab has identified hundreds of new disease genes causing known or previously undescribed diseases. These include de novo mutation of large numbers of genes that cause congenital diseases, including malformations of the heart, the fusion of skull bones that prevent normal brain growth (craniosynostosis), and autism. Unexpectedly, mutations in chromatin modifiers are major contributors to both congenital heart disease and autism, explaining the frequent co-occurrence of these traits.

The lab has also developed methods to identify genes with incomplete penetrance, including new telomere maintenance genes for pulmonary fibrosis (e.g., *PARN*) that require inhalational exposure for disease expression; and rare mutations in *SMAD6* that have low penetrance for craniosynostosis without the presence of a common *BMP2* risk allele.

Similarly, the lab has been able to dissect a number of previously unsolved problems, including mutations that cause a variety of primary cancers and determinants of metastatic disease; and single mutations that cause hormone-producing tumors and diverse skin diseases.

In the case of hypertension, the most frequent global cause of death, Lifton has shown that mutations that cause extremely high or low blood pressure act by modulating renal salt reabsorption, providing the scientific basis for global efforts to reduce cardiovascular mortality by altering salt balance. Recent studies have shown that adrenal tumors that constitutively produce aldosterone—a common cause of severe hypertension—arise from single somatic mutations in a potassium ion channel that causes cell proliferation and hormone production. Chemical screens have identified macrolides that selectively inhibit mutant channels, providing new opportunities for the diagnosis and treatment of these tumors. Genetic studies also identified a new physiologic pathway regulating the balance between salt reabsorption and potassium ion secretion. Biochemical studies have revealed the mechanisms that regulate this balance, which explains how increased dietary potassium lowers blood pressure.

These results collectively demonstrate a path to determine the consequence of mutation of every gene in the human genome, showing that much more genomic discovery lies ahead than behind.

EDUCATION

B.A. in biological sciences, 1975
Dartmouth College

M.D., 1982
Ph.D. in biochemistry, 1986
Stanford University

MEDICAL TRAINING

Residency, 1983–1986
Chief Medical Resident, 1986–1987
Brigham and Women's Hospital

POSITIONS

Instructor in Medicine, 1986–1990
Assistant Professor, 1991–1993
Harvard Medical School

Assistant Professor, 1993–1994
Associate Professor, 1994–1997
Professor, 1997–2016
Chair, Department of Genetics, 1998–2016
Director, Yale Center for Human Genetics and Genomics, 1998–2016
Founder, Executive Director, Yale Center for Genome Analysis, 2009–2016
Yale University School of Medicine

Investigator, 1994–2016
Howard Hughes Medical Institute

Professor, 2016–
President, 2016–
The Rockefeller University

AWARDS

Homer Smith Award, American Society of Nephrology, 1998

Claude Amiel Award, International Congress of Nephrology, 1999

Novartis Award for Hypertension Research, American Heart Association, 1999

Pasarow Award for Cardiovascular Research, 2001

Richard Bright Award, American Society of Hypertension, 2002

Basic Research Prize, American Heart Association, 2002

Roy O. Greep Award, The Endocrine Society, 2003

Distinguished Scientist Award, American Heart Association, 2005

Robert Tigerstedt Award, International Society of Hypertension, 2006

A.N. Richards Award, International Society of Nephrology, 2007

Wiley Prize, 2008

Breakthrough Prize, 2014

Kornberg–Berg Lifetime Achievement Award, Stanford University, 2015

New York Academy of Medicine Medal for Biomedical Science, 2016

George M. Kober Medal, Association of American Physicians, 2023

HONORARY SOCIETIES

National Academy of Sciences

National Academy of Medicine

American Academy of Arts and Sciences

SELECTED PUBLICATIONS

Timberlake, A.T. et al. Two locus inheritance of non-syndromic midline craniosynostosis via rare *SMAD6* and common *BMP2* alleles. *Elife* 5, e20125 (2016).

Choi, J. et al. Genomic landscape of cutaneous T cell lymphoma. *Nat. Genet.* 47, 1011–1019 (2015).

Zaidi, S. et al. De novo mutations in histone-modifying genes in congenital heart disease. *Nature* 498, 220–223 (2013).

Boyden, L.M. et al. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature* 482, 98–102 (2012).

Choi, M. et al. K^+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* 331, 768–772 (2011).