

“Design and Analysis of Human DNA Sequence-based Association Studies”

NICHOLAS SCHORK, PHD

DIRECTOR OF BIOSTATISTICS AND BIOINFORMATICS,

DIRECTOR OF RESEARCH

THE SCRIPPS TRANSLATIONAL SCIENCE INSTITUTE

SCRIPPS GENOMIC MEDICINE, SCRIPPS RESEARCH INSTITUTE

LA JOLLA, CA

ABSTRACT

The limitations of genome-wide association (GWA) studies that focus on the phenotypic influence of common genetic variants have motivated human geneticists to consider the contribution of rare variants to phenotypic expression. The increasing availability of high-throughput sequencing technology has enabled studies of rare variants, but such technology will not be sufficient for the success of these studies since appropriate analytical methods are also needed. We evaluate the intuitions and modeling constructs behind many statistical analysis approaches to testing associations between a phenotype and collections of rare variants in a defined genomic region or set of regions. We also apply these methods to actual sequence data in an effort to showcase their utility and limitations. In addition, we emphasize the need to integrate functional genomic annotations into relevant statistical analyses in addition to being sensitive to the fact that humans are diploid and hence possess two genomes. Ultimately, although a wide variety of analytical approaches exist, more work is needed to refine them, make them more biological relevant and determine their properties and power in different contexts.