The detection of regulatory sequence variants involved in human disorders

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The convergence of high-throughput technologies for sequencing individual exomes and genomes and rapid advances in genome annotation are driving a neo-revolution in human genetics. This wave of family-based genetics analysis is revealing causal mutations responsible for striking phenotypes. By mapping the reads to the human genome reference and by searching for variations relative to the reference, a list of small nucleotide variations and structural variations is obtained. Analysis is required to reveal those variations most likely to contribute to a disease phenotype within a family. Existing software score the severity of changes that arise in protein encoding exons. However, most mutations within a family are situated in the 98% of the genome that controls the developmental and physiological profile of gene activity - the sequences that control when and where a gene will be active.

Functional contributions of cis-regulatory sequence variations to human genetic disease are numerous. With full genome sequencing becoming accessible to medical researchers, the need to identify potential causal mutations in regulatory DNA is becoming imperative. We are implementing a software system to enable genetics researchers to characterize regulatory DNA changes within individual genome sequences. We are combining reference databases of known regulatory elements, experimental archives of protein-DNA interactions and computational predictions within an integrated analysis package. With our software, researchers will have greater capacity to identify variations potentially causal for disease.