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Title: The Genetic Complexity of the Human Genome in Health and Disease

The Human Genome Project refers to the determination of the DNA sequence of the 23 chromosome pairs- the haploid genome consists of $3x10^9$ base pairs-and the small molecule of the mitochondrial DNA in humans. Completion of the Human Genome Project's sequencing effort , was announced in 2003 by *The Human Genome Project* and the *Celera Corporation* and this opened up the way of a deeper understanding of cell function in health and disease. The Human Genome contains specific DNA entities: genes are in the area 19.000-20.000, protein-coding sequences represent a very small fraction (approx.1.5%), while the rest of the genome is associated with introns, regulatory DNA sequences, repetitive DNA sequences, non-coding RNA genes and sequences of yet unknown function. Genome architecture is facilitated by specifiic genome organisers and gene 'landscapes' have been identified with reference to complex cell processes, eg the Development, as well as to multifactorial diseases eg Cancer, advancing our understanding of their physiology and their interconnections.

Whole genome sequencing (WGS) or whole exon sequencing (WES) refer to the analysis of multiple genes in a single test that may identify the several hundreds of coding variants in the genome of specific, disease cells in a person, that are potentially pathogenic. The main challenge is to understand which of these variants are relevant to a specific patient's disease and to this end considerable computing power and proper 'control' cell-populations are needed. Genome- wide association studies (GWAS) are an extension of the WGS studies, in that they involve the testing of genetic variants across the genomes of a high number of individuals, in order to identify genotype–phenotype associations. GWAS have revolutionize the study of complex traits and diseases by identifying novel disease susceptibility genes and by producing an ever increasing number of compelling genetic associations that are already translated into clinical care. These efforts have lead to Precision Medicine, a part of the Personalized Medicine, which aims at treating the patient rather than the disease.

The accessibility of whole genomes sequences, along with the technological progress, has contributed greatly to the growth of parallel scientific fields. Within this context, it advanced the study of the 3-dimentional level of gene transcription, as a means of uncovering essential elements of the expression of complexes of genes that are subjected to co-regulation, eg the hemoglobin genes. And in the case of cell modification for gene therapy applications, it is providing the basis for toxicity testing, as gene transfer is mostly carried out by viral vectors, whose DNA, after entry, is incorporated into the genome, in the nucleus of the recipient cell. The insertion of the vector DNA into the host genome may interfere with the normal gene expression program of the modified cell, causing toxicity.

Unravelling and exploiting the genetic complexity of the human genome has indeed introduced a new dimension in our perspective of the human biological processes in health and disease.