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   Sommario/riassunto A "genotype"" is essentially an organism's full hereditary information which is obtained from its parents. A ""phenotype"" is an organism's actual observed physical and behavioral properties. These may include traits such as morphology, size, height, eye color, metabolism, etc. One of the pressing challenges in computational and systems biology is genotype-to-phenotype prediction. This is challenging given the amount of data generated by modern Omics technologies. This "Big Data" is so large and complex that traditional data processing applications are not up to the task. Challenges arise in collection, analysis, mining, sharing, transfer, visualization, archiving, and integration of these data. In this Special Issue, there is a focus on the systems-level analysis of Omics data, recent developments in gene ontology annotation, and advances in biological pathways and network biology. The integration of Omics data with clinical and biomedical data using machine learning is explored. This Special Issue covers new methodologies in the context of gene-environment interactions, tissue-specific gene expression, and how external factors or host genetics impact the microbiome.