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Genomic Data in Drug Discovery and Early Research

An Overview of Genomic Data Use Cases and Case Studies

The Role of Genomic Data in Drug Discovery and Early Research

Genomic and multi-omic data has become an increasingly important tool in the discovery and early research stages of drug development. By analyzing the relationship between an individual's genome or omic profile and clinical phenotype, researchers are able to better understand the underlying causes of diseases and identify potential therapeutic targets. In addition, linked omic and phenotype data can be used to predict which patients are likely to progress in a disease condition or respond to a particular treatment, accelerating development and leading to more personalized and effective medicine. As a result, the use of genomic data in discovery and early research is revolutionizing the way we approach the treatment of diseases. We have already seen practice-changing precision medicines in Oncology come to market and broad use of oncology genomic data in drug development, but have yet to reach maturity of genomic applications in other disease areas like cardiometabolic and autoimmune disease.

Case studies span autoimmune and cardiometabolic disease areas such as:

- **Chronic Liver Disease**
- **Inflammatory Bowel disease**
- **Congenital Heart Disease**
- **Systemic Lupus Erythematosus**

This eBook delves into 6 specific use cases in which genomic data can be applied to the discovery and study of new therapeutics and shares some examples of how this is being done in autoimmune and cardiometabolic disease areas.

01 Biomarker Discovery

What You Need to Know

Omic data linked with clinical phenotypic data can be used to identify candidate biomarkers for a wide range of diseases. By analyzing an individual's genome, researchers can identify genetic variations associated with a particular disease or phenotypic outcome. These variants can be used as biomarkers for early detection and diagnosis as well as potential targets or prognostic measures for therapeutic development.

CASE STUDY

Read the Article

Biomarker Discovery for Chronic Liver Diseases by Multi-Omics - a Preclinical Case Study

Daniel Veyel | January 28, 2020 | Scientific Reports vol. 10

Research Takeaways

This study used RNA-Seq and proteomics to analyze liver samples from rats fed a choline-deficient L-amino acid-defined diet, a known NASH model, to determine relevant molecular pathways and correlations between mRNA and protein changes. Using plasma proteomics, they identified known human markers and novel candidates, and used regression analysis to demonstrate that the top-ranked markers were highly predictive of fibrosis in the rat model. The authors believe that their multi-omics approach, which combined plasma proteomics with liver histology and prior knowledge, could be applied to human biomarker discovery.

CASE STUDY

Read the Article

A Modular Analysis Framework for Blood Genomics Studies: Application to Systemic Lupus Erythematosus

Damien Chaussabel | July 18, 2008 | Immunity vol. 29

Research Takeaways

The researchers used microarray analysis to identify transcriptional modules, which are formed by genes coordinately expressed in multiple disease data sets. They found that mapping changes in gene expression at the module level generated disease-specific transcriptional fingerprints that provide a stable framework for the visualization and functional interpretation of microarray data. These transcriptional modules were used as a basis for the selection of biomarkers, and the researchers developed a multivariate transcriptional indicator of disease progression in patients with SLE.

02 Target Identification and Validation

What You Need to Know

Genetic or transcriptional variants associated with a particular disease can be targeted by the development of new drugs. Additionally, target validation can also involve functional assays to demonstrate that the target is biologically active and can be modulated by the drug, which can further increase the chances of success in clinical trials. Genomic data can be used to help identify targets that are more likely to be effective for specific populations.

CASE STUDY

Genome-Wide Analysis of 53,400 People with Irritable Bowel Syndrome Highlights Shared Genetic Pathways with Mood and Anxiety Disorders

Daniel Veyel | January 28, 2020 | Scientific Reports vol. 10

Read the Article

Research Takeaways

In this case study, researchers conducted a genome-wide association study using data from 53,400 people with irritable bowel syndrome (IBS) and 433,201 controls. They found six genetic susceptibility loci for IBS and replicated their findings in an independent cohort. The identified genes, which include NCAM1, CADM2, PHF2/FAM120A, DOCK9, CKAP2/TPTE2P3, and BAG6, are associated with mood and anxiety disorders, expressed in the nervous system, or both. The study also found a strong correlation between the risk of IBS and anxiety, neuroticism, and depression, suggesting that there are shared pathogenic pathways underlying IBS. This highlights the importance of considering the brain-gut interactions in the pathophysiology of IBS and the potential for targeted therapies that address both the gut and the brain.

03 Disease Mechanism of Action

What You Need to Know

Omics data can be used to understand the biological processes and pathways that lead to the development and progression of a particular disease and the genetic factors that contribute to this disease development. The disease mechanism of action may involve:

- Genetic and environmental factors
- Changes in cellular signaling pathways
- Dysfunction of specific organs or tissues
- Disruptions in normal physiological processes

Additionally, transcriptomic data can be used to study the expression of genes in different tissues and at different stages of the disease, providing insight into the disease's progression over time.

CASE STUDY

The Influence of the Proinflammatory Cytokine, Osteopontin, on Autoimmune Demyelinating Disease

Dorothée Chabas | November 23, 2001 | Science vol. 294

Read the Article

Research Takeaways

Researchers in this study aimed to use genomic data to understand a mechanism of action behind multiple sclerosis (MS). This study found that a protein called osteopontin is present in high levels in the brains of people with MS and in rats with a similar condition. When mice without osteopontin were tested, they were less likely to develop the disease and had more frequent recoveries. This suggests that osteopontin plays a role in MS and might be a target for treating the disease. The authors suggest that osteopontin may have pleiotropic functions in the pathogenesis of demyelinating disease in MS, and may even protect the axon from degeneration. Human genomic data could be used to confirm results seen in rodent genomic studies.

04 Pharmacogenetics and Dosing

What You Need to Know

Pharmacogenomics research is aimed at understanding how an individual's genetic makeup affects their response to drugs. Genomic data can be used to identify variations in genes that encode drug targets, drug-metabolizing enzymes, and drug transporters. These variations can affect the way a person metabolizes a drug, leading to differences in drug efficacy, toxicity, and side effects between individuals.This information can be used to optimize dosing, to predict potential side effects and prevent drug-drug interactions.

CASE STUDY

Pharmacogenetics in Inflammatory Bowel Disease: Understanding Treatment Response and Personalizing Therapeutic Strategies

Read the Article

Jesús K. Yamamoto-Furusho | May 26, 2017 | Pharmacogenomics and Personalized Medicine vol. 10

Research Takeaways

This article is a review of pharmacogenomic drivers of treatment response in IBD patients. One study mentioned in this article assesses the multidrug-resistant (MDR1) gene code for a drug efflux pump P-glycoprotein-170 (permeability glycoprotein or Pgp), which is expressed on the surface of lymphocytes and intestinal epithelial cells and functions to actively transport toxins and drugs out of target cells. Pgp and MDR expression have been shown to be significantly higher in Crohn's Disease and Ulcerative Colitis patients requiring surgery due to failure of medical therapy which could lead to slower transport of drugs out of target cells and impact patient outcomes.

05 Predicting Disease Risk

What You Need to Know

Knowing the details of an individual's genome, especially when combined with that individual's clinical history, can help researchers identify specific genetic variations that are associated with a higher risk of a disease and interventions that can be implemented to prevent or delay the onset of the disease, such as lifestyle changes or regular screenings.

CASE STUDY

Congenital Heart Disease Risk Loci Identified by Genome-Wide Association Study in European Patients

Harald Lahm | January 19, 2021 | The Journal of Clinical Investigation vol. 131

Read the Article

Research Takeaways

The study involved 4,034 patients with CHD and 8,486 healthy controls, and identified several single SNPs on different chromosomes that are associated with specific CHD phenotypes. One SNP on chromosome 5q22.2 reached genome-wide significance across all CHD phenotypes and was also indicative for septal defects. The study also performed a functional analysis of the SNP-carrying genes and found that they play an essential role in heart development. This research provides insights into the genetic basis of CHD and demonstrates the potential of genomic data in predicting disease risk.

06 Patient Stratification

What You Need to Know

By analyzing an individual's genome, researchers can identify genetic variations that are associated with a particular disease or response to a treatment. This information can be used to:

- Group patients with similar genetic profiles
- Tailor treatment options to specific groups of patients
- Understand the underlying mechanisms of a disease for subpopulations of patient cohorts

Genomic patient stratification in drug development helps to improve personalization of the diagnosis, treatment, and prevention of diseases for targeted populations.

CASE STUDY

Genetic Predictors of Medically Refractory Ulcerative Colitis

Talin Haritunians | November 1, 2011 | Inflammatory Bowel Diseases vol. 16

Read the Article

Research Takeaways

The authors used 46 distinct single nucleotide polymorphisms (SNPs) to define four colectomy risk groups with risk scores based on the number of risk alleles in the patients (ranging between 0–92 i.e. 46 SNPs, 2 alleles) in a cohort of 929 refractory UC patients. 100% of patients in "risk group D" with the highest risk score required colectomy, whereas only 0.9% of colectomy cases were in risk group A, which had the lowest risk score. This study demonstrated the use of genomic information to stratify UC patients with different risk scores and outcomes which could be used to target drug development for specific subpopulations.

Functional Assay

A laboratory test that is used to measure the activity or function of a specific protein, gene or molecule in order to determine its involvement in a biological process or disease.

Genome-wide association study

A method used to identify genetic variants associated with a particular trait or disease by comparing the genomes of individuals with the trait or disease to those without.

Microarray analysis

A technique used to measure the expression levels of thousands of genes simultaneously by using a small sample of DNA or RNA.

Multi-omics

A biological analysis where the data sets of different omic groups, such as genome, proteome, transcriptome, epigenome, or microbiome, are combined to more comprehensively measure gene expression, gene activation, and protein levels.

Multivariate transcriptional indicator

Sets of genes that are coordinately expressed in multiple disease data sets, this can be used as a basis for the selection of biomarkers.

Pathogenic pathways

Biological pathways that lead to the development of a disease or disorder.

Proteomics

The large-scale study of proteomes, or the set of proteins produced in an organism, system, or biological context.

SNP (Single Nucleotide Polymorphism)

A single nucleotide polymorphism (SNP) is a type of genetic variation where a single nucleotide (A, T, C, or G) in a DNA molecule differs between individuals in a population.

Susceptibility loci

A specific location in the genome associated with a higher risk of developing a certain disease

Transcriptional modules

Sets of genes that are coordinately expressed in multiple disease data sets, this can be used as a basis for the selection of biomarkers.

Transcriptome

A transcriptome is the full range of messenger RNA molecules expressed by an organism. In contrast with the genome, which is characterized by its stability, the transcriptome actively changes.

Whole Genome Sequencing

A laboratory process that is used to determine nearly all of the approximately 3 billion nucleotides of an individual's complete DNA sequence, including non-coding sequence.

Looking to the Future

With advancements in whole genome sequencing, and other omics data generation and analysis techniques, the world is fast approaching a major transformation in how healthcare is researched and delivered. The opportunities across diseases with unmet patient need are numerous.

However, there are a number of challenges that we still face in accessing the genomic data needed to realize this vision.

- The availability of tissue varies greatly across disease areas, with more biopsied tissue collected as standard or care in oncology than other diseases
- Cohort sizes for rare conditions remain small and phenotypic data associated with genomic data can lack depth without strong linkages to established datasets.
- Genomic data samples over-represent patients of European ancestry and those that seek care at academic medical centers which leads to a lack of diversity in genomics research and drug development.
- Pharma companies and drug researchers have difficulties in accessing and using omics data - the operational burden in getting access to samples from disparate biobanks and lab sources is a barrier and bioinformatics talent remains hard to find.
- The cost and capabilities required to analyze large amounts of genomic data are insufficient
- Large-scale genomic studies can be expensive and time-consuming, and require specific expertise.

Overall, the potential applications of genomic data in research are vast and varied, and will continue to grow as the technology improves and our understanding of genetics deepens.

Ovation Helps Advance Genomic Data Use Cases

In a time where genomic data is actively and more regularly being applied to early drug discovery and pre-clinical research, Ovation's ability to coordinate across labs, sequencing partners and phenotypic data vendors to deliver high quality, 30-50x whole-genome sequenced cohorts, whole exome sequencing and transcriptomics (where tissue is available) can alleviate many of the challenges researchers have with obtaining genomic data. Ovation is committed to providing researchers with access to a diverse collection of omics datasets at scale sourced from a network of labs that are representative of the US population.

Ovation has biobanked over 1.38M samples consented for research and commercial purposes, that can be sequenced using state of the art technology with our lab partners.

Ovation helps researchers access high-quality genomic data linked to rich, longitudinal phenotypic data at scale which enables life sciences to advance drug discovery and development more efficiently.

About Ovation

Ovation is a leading provider of genomic data for the life sciences industry. We are dedicated to supporting the advancement of precision medicine and offer access to a wide range of high-quality, consented genomic data linked to diverse, longitudinal phenotypic data. Our data allows researchers to identify and validate biomarkers, discover new targets and understand resistance mechanisms in various populations.

Learn more at ovation.io →

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Contact Ovation today to learn more about how our deep genomics data can help you achieve your research goals.

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