Biochimica et Biophysica Acta 1842 (2014) 1903–1909

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Systems genetics: From GWAS to disease pathways ☆

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ARTICLE INFO

Article history:
Received 2 September 2013
Received in revised form 21 March 2014
Accepted 27 April 2014
Available online 2 May 2014

Keywords:
Post-GWAS
Systems genetics
Integrative approach
Disease mechanism
Network modelling
Causal inference

ABSTRACT

Most common diseases are complex, involving multiple genetic and environmental factors and their interactions. In the past decade, genome-wide association studies (GWAS) have successfully identified thousands of genetic variants underlying susceptibility to complex diseases. However, the results from these studies often do not provide evidence on how the variants affect downstream pathways and lead to the disease. Therefore, in the post-GWAS era the greatest challenge lies in combining GWAS findings with additional molecular data to functionally characterize the associations. The advances in various ~omics techniques have made it possible to investigate the effect of risk variants on intermediate molecular levels, such as gene expression, methylation, protein abundance or metabolite levels. As disease aetiology is complex, no single molecular analysis is expected to fully unravel the disease mechanism. Multiple molecular levels can interact and also show plasticity in different physiological conditions, cell types and disease stages. There is therefore a great need for new integrative approaches that can combine data from different molecular levels and can help construct the causal inference from genotype to phenotype. Systems genetics is such an approach; it is used to study genetic effects within the larger scope of systems biology by integrating genotype information with various ~omics datasets as well as with environmental and physiological variables. In this review, we describe this approach and discuss how it can help us unravel the molecular mechanisms through which genetic variation causes disease. This article is part of a Special Issue entitled: From Genome to Function.

1. Introduction

Over the last 5–10 years enormous progress has been made in identifying genetic variants underlying various phenotypes, including different complex diseases and complex traits. Genome-wide association studies (GWAS), which aim to correlate allele frequencies of single nucleotide polymorphisms (SNPs) with a disease status or trait variation in a human population, have now become a standard tool in human genetics research [1]. At the moment (March 2014), 1818 GWAS papers have been published describing 12,498 associations, as listed in the GWAS catalogue of the National Human Genome Research Institute (www.genome.gov/gwastudies/) [2]. And new loci are still being discovered. From a medical perspective, the ultimate goal of GWAS is to identify the causal variants of a phenotype, their functional effects and the biological pathways through which they operate in complex disease pathogenesis. However, although thousands of phenotype-associated loci have been identified, the molecular mechanisms through which they act are still largely unknown. In practice, the interpretation of GWAS findings is complicated by the fact that most identified associations are part of a larger region of correlated variants. SNPs in close proximity can be in strong linkage disequilibrium with each other, making it hard to pinpoint the causal variant. Furthermore, the majority of identified SNPs are annotated outside of protein-coding genes, indicating that the underlying mechanism is most likely regulatory. This makes it more challenging to elucidate the direct functional consequences of the variants.

The lack of explanatory power of GWAS thus calls for additional methods to uncover the mechanisms that underlie complex diseases. Over the last few years, different approaches have been explored to discover functional relationships between genes at the associated loci, for instance, by searching for genes with similar functions or within the same molecular pathway [3–5]. One widely used approach is the gene set enrichment analysis, which determines whether an a priori defined set of genes is statistically enriched for disease associations. Many tools

☆ This article is part of a Special Issue entitled: From Genome to Function.

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http://dx.doi.org/10.1016/j.bbadis.2014.04.025
0925-4439/

have been developed to combine GWAS findings with GO terms [6,7], protein–protein interactions [8], information from pathway databases, such as the Kyoto Encyclopaedia of Genes and Genomes (KEGG) [9,10], or co-occurrence/co-citation in the literature [11]. Although these methods have proven successful in prioritizing candidate genes and identifying overrepresented pathways, they tend to be heavily biased by the extent of prior knowledge available (including functional annotation and curated information). Many disease-associated candidate genes that lack prior biological pathway annotation, will unintentionally 'miss the mark' using these annotation-based enrichment methods.

The past few decades have witnessed an enormous growth in the quantity, quality, diversity and richness of human molecular and functional data being generated. The advances in high-throughput technologies have enabled large-scale profiling of the transcriptome, proteome, metabolome, epigenome and microbiome across multiple disease states, phenotypes, perturbation conditions and/or cell types. These ~omics profiling approaches can be used not only to evaluate and monitor the change of individual biomolecules in diseases, but also to investigate the genetic basis of inter-individual variation for the molecular traits. Systems genetics, which evaluates this genetic basis, aims to reveal the genetic flow from DNA to the phenotype through intermediate molecular traits. This strategy has been proposed as a powerful method to investigate the molecular mechanisms underlying complex traits and diseases [12,13]. To do so, the experimental design and analysis framework can include multiple steps (Fig. 1): 1) association studies or linkage analysis to identify genetic loci that underlie complex traits and diseases; 2) genomics analysis to profile ~omics data and identify the biomolecules that are of relevance; 3) genetical genomics studies to investigate the effect of genetic variants on multiple intermediate molecular phenotypes and to illustrate the genetic variation of molecular traits; and 4) network modelling and causal inference analysis to construct the molecular circuitry from genotype to phenotype. In this review, we describe how systems genetics can help close the gap between genotype and phenotype. We focus on the genetic variation of molecular traits and their dynamics (step 3) and on network modelling and causal inference analysis (step 4) to illustrate how systems genetics can provide the systems-wide view on disease aetiology that is urgently needed for effective diagnosis and development of therapeutic interventions.

2. Genetic variation of molecular traits

Genetic loci can enforce their risk via intermediate molecular traits, such as gene expression, proteins and metabolites, resulting in inter-individual variation of biomolecules that is under genetic control. A molecular trait can therefore be viewed as a quantitative trait and used in genome-wide association studies in natural populations or linkage analyses in segregating populations. By using these genetical genomics analyses, the genomic locus underlying the variation in the measured trait, called quantitative trait locus (QTL), can be identified [14]. The first genome-wide genetic analysis on gene expression was performed in haploid yeast segregants [15] and this proof-of-concept analysis demonstrated a widespread genetic effect on gene expression. Subsequent studies were carried out in many different organisms, including humans [16–20], and on other molecular levels, such as proteins [21–23], metabolites [24–26] and methylation [27,28]. These studies have greatly increased our knowledge of the functional consequences of genetic variants.

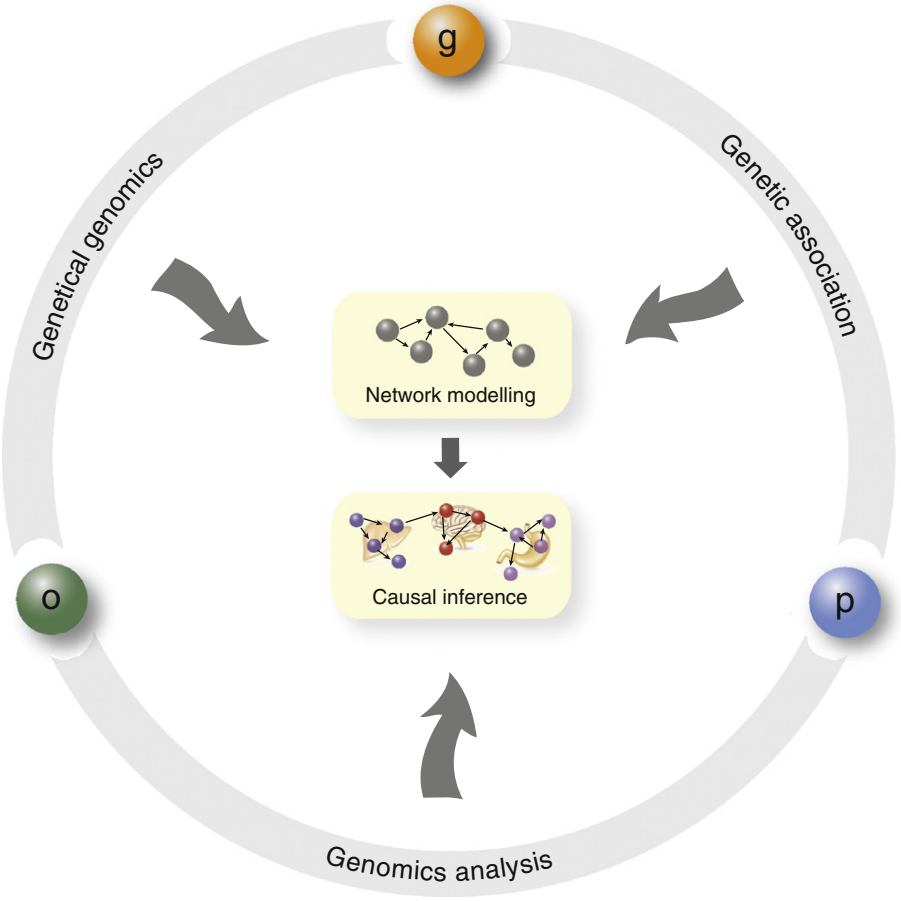

Fig. 1. The systems genetics approach. Systems genetics combines genetical genomics, genetic association and genomics analyses to construct the causal inference from genotype to phenotype. The approach integrates genotype information (g) with large-scale ~omics profiling data (o) and phenotype data (p) and can be used to build a network and infer causality for the different relationships.

2.1. Expression QTL analysis

As transcripts are the first direct products of DNA, defining the genetic variation on gene expression can provide crucial functional information on genetic variation. The genomic loci that underlie variation in gene expression are called expression quantitative trait loci (eQTL). Based on the physical distance between the eQTL and the affected gene, the eQTL can be classified as *cis*-eQTL or *trans*-eQTL. A *cis*-eQTL refers to a SNP and a gene that are in the vicinity of each other (commonly within a distance of 250 kb to 1 Mb in natural populations and 1–5 Mb in segregating populations) [29,30], while *trans*-eQTLs are SNP-gene pairs that are further away from each other or which may even lie on different chromosomes. eQTL analysis can have different implications for interpreting GWAS associations and constructing networks, for instance *cis*-eQTLs can help to prioritize causal variants and candidate genes at disease-associated loci. Over 40% of disease-associated SNPs are observed to have a *cis*-acting effect on gene expression [31,32]. Based on this reasoning, the *cis*-eQTL has been successfully used to select the novel but weak associations that do not pass the genome-wide significance level in GWAS, thereby bypassing the need to increase the sample size [33,34]. Another important potential advantage of studying eQTLs is that they can provide insight into the disease mechanism and underlying pathways. *Trans*-eQTLs can affect downstream disease genes which were not identified by GWAS before and are becoming increasingly important to resolve the molecular pathways leading to disease [35]. However, a systematic identification of *trans*-eQTLs is challenging, as a *trans*-eQTL is believed to be an indirect association and has a smaller effect than a *cis*-eQTL. Due to the robustness of biological systems and the theory of phenotypic buffering, molecular factors located further downstream in the pathway tend to have a smaller effect than the factors upstream [36]. Recent advances in the development of statistical frameworks for *trans*-eQTL analysis [37] and the dramatically increased sample size [38] now allow for a systematic identification of *trans*-eQTLs, providing insight into the downstream effects of trait-associated variants. A recent systematic *trans*-eQTL analysis in 8086 human individuals has reported *trans*-effects for 233 disease-associated SNPs [38]. One striking example is a SNP associated with systemic lupus erythematosus (SLE). This SNP was found not only to affect the expression of the transcription factor *IKZF1* (IKAROS family zinc finger) in *cis*, but it also affects the expression of 10 different genes in *trans*, including four genes involved in the complement system and six in type 1 interferon response. Both of these processes are important for SLE. This study demonstrated the power of *trans*-eQTL analysis in identifying key regulators of disease and their downstream effects.

2.2. Genetic effects can propagate to different molecular levels

Expression quantitative trait locus studies have proven to be powerful in functional genomics. But in order to gain a full picture of the disease process, it is important to study how genetic variation propagates from DNA to transcripts and further to other ~omics levels, such as proteins and metabolites. The success of eQTL studies suggests that there is a potential value in applying the QTL approach to other molecular traits as well. For example, Melzer et al. evaluated the role of genetic variation on the levels of 42 proteins measured in 1200 individuals [21]. They detected *cis*-effects for eight proteins and *trans*-effects for one protein. Six of these eight proteins correlated with inflammatory or metabolic pathways and provided a mechanistic view on the disease process. On the metabolism level, the most studied trait would be blood lipid levels and up to date 157 loci have been robustly established [39,40]. These loci account for ~10–20% of the variation in blood lipids and often underlie susceptibility to many cardiovascular and metabolic traits. With the developments in high-throughput technologies, like nuclear magnetic resonance (NMR) and mass spectrometry, an increasing number of protein and metabolites can be quantified. This was demonstrated by Karsten Suhre's group, who conducted a comprehensive and systematic evaluation of genetic variance in blood metabolism. They analysed over 250 metabolites in serum samples, thereby advancing our knowledge of the molecular basis for many metabolic diseases [25,41]. An example of a locus that was found to be associated with blood metabolite concentrations is the *FADS1* gene (fatty acid desaturase 1). This locus is also associated with multiple complex diseases and traits, including inflammatory bowel disease [42,43], heart rate [44], insulin resistance and type 2 diabetes [45,46]. Genetic variants in this gene were observed to have a modest effect on the expression of *FADS1* [38] as well as on blood HDL cholesterol, LDL cholesterol and triglyceride levels [47]. Their strongest effect was seen on phospholipids, explaining up to 40% of the observed variation for this trait [41]. This finding suggests that investigating the genetic effect on multiple molecular levels can provide a system-wide view on the downstream effects of disease-associated SNPs and subsequent mechanistic insights into the disease aetiology.

3. Dynamics of genetic variation

Genetic variants are observed to have a dynamic effect, depending on the cell-type, tissue-type, developmental stage or environmental condition [48,49]. Several studies have estimated the proportion of *cis*-regulated gene expression specific to certain cell-types [50–52] or tissues [53–56]. Although most *cis*-eQTLs show a concordant association across different samples, a substantial proportion exerts a specific effect. For example, Ding et al. found a difference in *cis*-eQTLs of only 1–5% when comparing psoriatic skin samples and healthy skin samples, but a difference of 30% when they compared eQTLs between skin and lymphoblastoid cell lines (LCLs) [56]. Similarly, 27.8% of the *cis*-eQTL was found to be tissue-specific when comparing blood, liver, adipose tissues and muscle [55], while 29% appeared to be tissue-specific in a comparison study between LCLs, skin and fat tissue [54]. These discoveries have huge implications for disease studies, as they emphasize the importance of using gene expression data from tissues relevant for the disease under study. For instance, for type 2 diabetes (T2D), eQTL studies have mainly been focusing on liver, adipose tissue, muscle and pancreatic B cells, and it was shown that T2D-associated SNPs were enriched for *cis*-eQTLs in liver and adipose tissue [34]. Not only *cis*-eQTLs but also *trans*-eQTLs can exert cell-type or tissue-type specific effects. In a more recent study, T2D-associated SNPs were functionally characterized through *trans*-eQTL analysis in five different tissue types [57]. The authors found an enrichment of a tissue-specific *trans*-effect for T2D SNPs. This suggested the downstream effect of T2D-associated genetic variants and the underlying pathways that may be active in the disease pathogenesis.

3.1. The role of the environment

Environmental factors also play an important role in shaping the genetic effect. Cadwell et al. [58,59] demonstrated that the interaction of genes and environment can determine disease phenotypes in the intestine. In a mouse model they found that the combination of an environmental trigger (a norovirus infection) and a genetic variant in the *ATG16L1* gene (a key gene involved in autophagy and previously associated with Crohn's disease) is required to generate the Paneth cell secretory abnormalities characteristic of Crohn's disease in human. There is also increasing evidence to indicate the important interplay between the gut microbiota and host genetics in disease. Patients with inflammatory bowel disease (IBD) and risk alleles in the IBD susceptibility genes *NOD2* and *ATG16L1* show altered intestinal microbiota compositions, with significant shifts in the frequencies of the *Faecalibacterium* and *Escherichia* taxa [60]. Host genetics may therefore substantially influence the structure and establishment of the gut microbiome [61]. Understanding the complex interactions between genetics and environmental factors would greatly benefit from a systems genetics approach. An example of this is a study by Parks et al., who examined

the genetic control of obesity and gut microbiota composition in mice in response to a high fat and sucrose diet [62]. Using a systems genetics approach, they combined GWAS and eQTL analyses with the systematic profiling of obesity traits and gut microbiota composition to assess gene–environment interactions, which would not have been possible with classic linkage studies or GWAS alone. Their findings showed that host genetics have a profound effect on shaping the plasticity of the gut microbiota in response to an environmental trigger. These examples thus illustrate the importance and promise of integrating genetic information with data from diverse multi-omics platforms towards delineating and understanding disease biology.

3.2. Longitudinal studies

In order to determine the pathways and networks that are activated during the onset and the development of diseases or during ageing, it can be valuable to monitor biomolecular levels over time. Current ~omics profiling efforts usually capture a snapshot of a set of molecules and their activity at defined time points. In order to establish the causal effects and their downstream events, it is important to also explore and take into account the time-delay or phase lag in the analysis of disease relations, such as with time-series analysis [63]. One of the first comprehensive and very promising longitudinal multi-omics studies has been the iPOP (integrative personal omics profiling) project led by Michael Snyder [64]. In this study, data was integrated from genomic, transcriptomic, proteomic, metabolomic and autoantibody profiles sampled from a single healthy individual over a 14-month period. First, the genome of the individual was sequenced and SNPs, indels and structural variants were determined. Based on these outcomes they assessed the genetic disease risk, revealing an elevated risk for coronary artery disease, basal cell carcinoma, hypertriglyceridemia and type 2 diabetes. Accordingly, next to the levels of transcripts, proteins and metabolites, markers associated with high-risk disease phenotypes were also monitored, such as glucose levels and HbA1c. One particularly striking observation was that an elevated glucose response onset was tightly associated with respiratory syncytial virus (RSV) infection. Although not yet proven, this observation has led to the interesting hypothesis that viral infections could perhaps trigger an altered glucose metabolic response that predisposes an individual to type 2 diabetes.

4. Network modelling and causal inference

It is clear that the underlying mechanisms of complex traits and diseases have a complex basis, where the phenotype can be the result of several genetic, molecular and environmental interactions. The next step is to develop and apply user-friendly computational algorithms to integrate and analyse the different phenotypic measurements and to gain a clear picture of the biological complexity [65].

4.1. Network modelling

Network reconstruction is a powerful and widely used approach that provides a flexible framework on which the complexity associated with biological pathways can be built systematically. A biological network depicts molecules (or a collection of molecules organized into functional modules) in a given biological system as nodes and their interactions as edges between the nodes. The edges can represent any type of relationship or association, such as regulation, physical binding, correlation or dependency between nodes. The reconstructed networks can incorporate curated information as well as data-driven relationships and can be inferred using different algorithms, including linear models, Bayesian approaches and equation-based methods [66,67]. Network modelling has been applied to a wide range of biological problems in the past few years, and has contributed to the discovery of several disease genes and biomarkers [68–71]. For example, Bordbar et al. used multi-omics data analysis (transcriptomics, proteomics and metabolomics) to construct a genome-scale metabolic network, which allowed them to determine metabolic modulators of macrophage activation [72]. Similarly, Tannahill and colleagues generated a metabolic map of lipopolysaccharide (LPS)-activated macrophages by combining metabolomic and transcriptomic data. They found that glycolytic genes were induced and were also correlated with expression profiles of the altered metabolites [73]. This led to the novel observation that succinate is an important (but previously under-appreciated) metabolite in innate immune signalling.

4.2. Inferring causality

When genetic information is incorporated into the network, it can support the inference of causality for the interactions among different traits. As genetic information flows from DNA to the intermediate phenotypes and eventually to the final phenotype (disease), there is a good indication that the disease-associated gene is also the causal gene when both the intermediate phenotype and the disease phenotype are associated with the same genetic variant. For example, such a strategy helped Musunuru and colleagues identify the *SORT1* gene as the causal gene underlying plasma LDL cholesterol and myocardial infarction [74]. By integrating eQTL data and lipid level measurements they found a liver-specific eQTL effect on the expression of the *SORT1* gene, suggesting a transcriptional regulatory role of the disease-associated SNP. The association of the same SNP with plasma LDL cholesterol also pointed towards a role in lipid processes. Functional analyses indeed confirmed the regulatory mechanism of modulating hepatic secretion of very low-density lipoprotein (VLDL).

When a disease-associated SNP is also found to affect a molecular trait, the causal relationship between the molecular phenotype and the disease phenotype is not directly clear. Several models are possible (Fig. 2): 1) the SNP can affect the molecular phenotype and the disease phenotype independently (independent model); or 2) the SNP can alter the molecular phenotype, which causes the development of disease (causal model); or 3) the SNP can cause the disease and in response to the disease status the molecular phenotype is changed (reactive model). Thus, to systematically construct the molecular pathway from genotype to phenotype, mathematical models and computational algorithms are needed to distinguish between the different models [75]. For example, Schadt et al. developed a likelihood-based causality model selection (LCMS) method for this [76]. In several succeeding studies they demonstrated the use of their LCMS model to identify obesity and atherosclerosis genes in mouse F2 populations [76–78]. Through the integration of DNA variation, gene expression and phenotypic information, the authors found that perturbations of predicted obesity genes resulted in significant changes in obesity-related traits [78]. In the atherosclerosis study, the LCMS model was used with mouse liver and adipose tissues, yielding hundreds of genes that tested as causal for aortic lesions [77]. One of these candidate causal genes, *C3ar1*, was experimentally validated using a mouse knockout model in the same study. Several causal genes were also found to be enriched for human cardiovascular disease-related SNPs identified by the Wellcome Trust Case Control Consortium [79]. These studies clearly demonstrate the effective use and power of statistical and mathematical models to identify causal relationships for complex diseases.

5. Challenges and future perspectives

Several studies have demonstrated the power of systems genetics in understanding disease aetiology. However, there are still major challenges to face and several considerations need to be taken into account when designing a systems genetics experiment.

The first challenge is the comprehensive acquisition of multi-dimensional in-depth phenotype data. At the moment, for many diseases, the data are scarce and heterogeneous in nature, making it difficult to study the dynamics of disease networks. Hence, the ideal

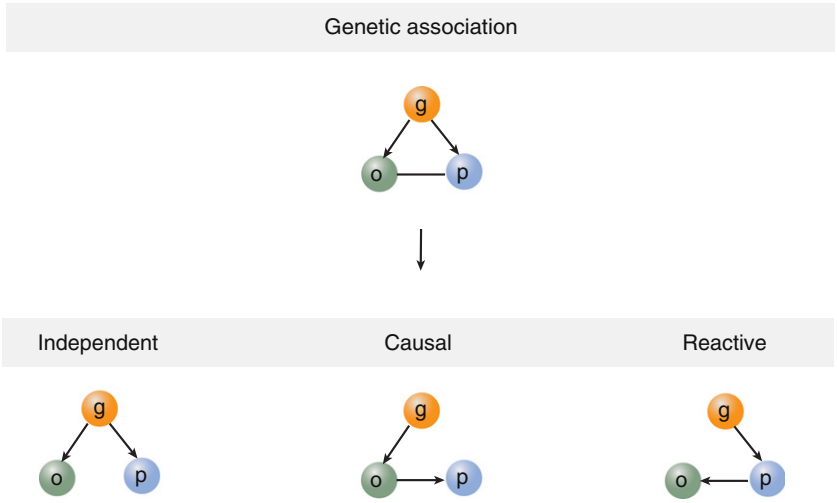

Fig. 2. Inference of causality. When two traits share a genetic association, statistical or mathematical models can be used to infer the relationship between the genotype (g), the molecular trait, represented by ~omics profiling data (o), and the phenotype (p). An association can be reactive, causal or independent. The correlation between the residuals of the traits, after accounting for genetic effects, can distinguish between the different causality models [76].

systems genetics experiment should facilitate the generation of data for the same individuals on multiple molecular levels and across different conditions and tissue types. Obviously, the economics of generating high-throughput data are an important factor here. Although the prices for these technologies are dropping fast, they will need to decline further in order to make longitudinal multi-omics studies readily affordable. It will be crucial for the years to come, to team up in consortia and use and combine the data that is publicly available in biobanks and databases. For instance, the Genotype-Tissue Expression (GTEx) programme of the Broad Institute (www.broadinstitute.org/gtex/) [80] aims to create a comprehensive public atlas of gene expression and regulation across multiple human tissues, and is a good first step in this direction. Likewise, in recent years, various prospective cohort studies have been set up, in which a group of individuals is followed over time, eventually making it possible to predict potential disease outcomes based on genetic risk, molecular biomarkers, physiological traits, and environmental factors [81-82, 69]. As demonstrated by the work of Michael Snyder's group, monitoring the development of potential diseases over time, combined with ~omics profiling, can provide a better understanding of the mechanism leading to disease [64].

The second challenge is related to the first and concerns the statistical power. In a systems genetics study, it is important to assess an adequate number of samples to get enough power for association testing. Although the sample size for GWAS and ~omics profiling has greatly increased over the past five years to include several thousands of samples, the number of samples can still be much lower than the number of factors tested at the genome-wide level (e.g., genetic factors or molecular factors). The result will be that, at the stringent significance level required to correct for multiple-testing, only the strong effects can be detected and more modest effects will be missed. In order to detect the more subtle effects, either the sample size needs to be increased dramatically or analysis approaches need to be applied to reduce the data complexity. Network analysis can also be of help here, as it can be used to cluster the separate factors into modules based on their function or their participation in a common biological process or pathway. Rather than examining the effect of individual molecules, such modelling allows one to examine the collective effect of groups of molecules, providing increased power.

A third challenge is the complexity of the causal inference. As more molecular phenotypes are measured, causative signals can be traced up and down a biological network. If variation can be determined at several of these phenotypic levels, then a proportion could be explained by the same genetic variant. As mentioned earlier, various mathematical models and algorithms can be used to characterize the relationships, such as linear regression modelling or Mendelian randomization [83]. However, causal relationships are expected to be much more complex than the models described in Fig. 2 [84]. Many confounding factors remain unknown or undetectable. As a result, more advanced mathematical models and algorithms have been proposed, including Bayesian networks [85] and structural equation modelling [86]. New methods need to be developed in the coming years that can take different assumptions for different data-types into account.

For genomics data to contribute to our understanding of disease biology we must first take the hurdle of integrating all the information that is now being generated. As we have discussed in this review, systems genetics has proven to be a promising approach to achieve this. In this respect, it is crucial to shift from the classical gene-centred view of disease biology to a network perspective, in which system-wide interactions in multiple cell types, tissues, organs and the environment together define the disease state. As systems genetics has the potential to generate these network-wide views on disease aetiology, it is likely to become a major tool in the development of personalized medicine and disease prevention in the near future.

Funding

M.S. and J.F. are supported by the Netherlands Organization for Scientific Research (NWO-VENI grant 863.09.007 to J.F.) and the Systems Biology Centre for Metabolism and Ageing (SBC-EBA grant 853.00.110). A.N. is supported by the Massachusetts General Hospital Department of Medicine investigator start-up funding.

Acknowledgements

We thank Jackie Senior for editing the manuscript.

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