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Genotype to phenotype via network analysis

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A prime objective of genomic medicine is the identification of disease-causing mutations and the mechanisms by which such events result in disease. As most disease phenotypes arise not from single genes and proteins but from a complex network of molecular interactions, *a priori* knowledge about the molecular network serves as a framework for biological inference and data mining. Here we review recent developments at the interface of biological networks and mutation analysis. We examine how mutations may be treated as a perturbation of the molecular interaction network and what insights may be gained from taking this perspective. We review work that aims to transform static networks into rich context-dependent networks and recent attempts to integrate non-coding RNAs into such analysis. Finally, we conclude with an overview of the many challenges and opportunities that lie ahead.

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Introduction

Genome-wide association studies (GWAS) have identified numerous risk loci for common complex diseases, and next-generation sequencing (NGS) based association strategies are now emerging to characterize the contribution of rare variants to human genetic disorders [1,2]. While these studies have provided useful insights into the heritability of diseases, prediction of disease risk from genetic information remains challenging. In addition, without a basic understanding of the biological mechanisms by which most of the candidate loci cause disease, it remains difficult to develop therapeutic strategies for countering them.

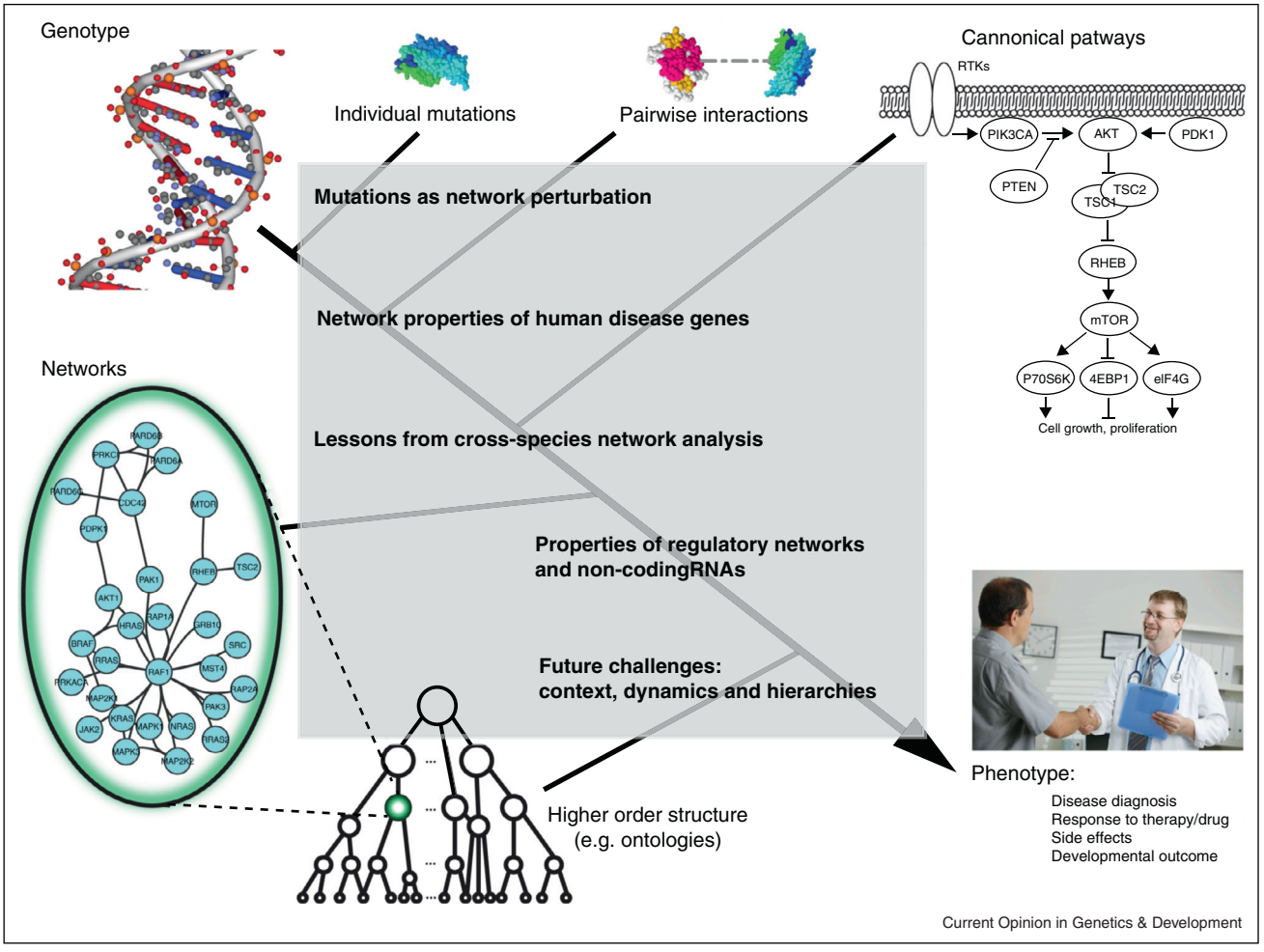
The phenotypic effects of genetic alterations result from disruptions of biological activities within cells. These activities arise from the coordinated expression and interaction of various molecules such as proteins, nucleic acids and metabolites [3–7]. Networks can provide a framework for visualizing and performing inference on the set of intracellular molecular interactions and are a promising intermediate for studying genotype–phenotype relationships.

In the ideal case, a candidate locus can be linked to phenotype using canonical 'pathways' curated from the biomedical literature, that is, sequences of experimentally characterized molecular interactions that give rise to a common function. For example, Lee *et al.* identified candidate *de novo* somatic mutations in cases of hemimegalencephaly (HME) [8] and found an enrichment of mutations in genes encoding key proteins in the canonical PIK3CA-AKT-mTOR pathway in the affected brain tissue. On the basis of structure of this well-studied pathway, they applied an assay to detect pathway activity downstream of the mutation events and determined that the *de novo* mutations were associated with elevated mTOR activity. Their findings further suggest that patients with HME may benefit from treatment with mTOR inhibitors.

In most cases, candidate genes implicated by GWAS or NGS-based studies are not well characterized and their products are not included in available canonical signaling pathways; furthermore, canonical pathways are likely to be incomplete and may even be inaccurate [7]. Systematic screens of the proteome suggest that canonical pathways capture only a fraction of the true protein–protein interactions that occur within the cell [9] and many such interactions may depend on tissue and condition-specific factors [10]. In addition, new classes of molecule such as microRNAs and lincRNAs are increasingly implicated in regulating the activity of protein coding genes [7,11–14].

In contrast to canonical pathways, network models are often built from systematic experimental screens, broad surveys of the literature or public databases of molecular interactions. These models can easily be extended to incorporate new molecular species or different types of relationship between molecules and represent essential tools for biological inference. Nonetheless, it is important to be aware that networks are subject to various ascertainment biases including those introduced by measurement

Figure 1



A hierarchical perspective of biological interactions mediating genotype–phenotype relationships. Protein activity is determined by protein amino acid sequence and structure. Proteins contribute to biological processes through interactions with other molecules in the cell. Biological processes arise from coordinated groups of molecular interactions, and in turn can interact to mediate higher order cellular behaviors and responses to environmental cues. Advances in several areas of network research are improving our understanding of how the organization of biological systems mediates genotype–phenotype relationships. This knowledge will be essential for identifying mutations underlying disease associations and their mechanisms of pathogenesis.

technologies, selection of proteins for systematic study or due to variation in the number of experiments or studies performed for particular genes.

Modeling genotype–phenotype associations will require understanding the consequences of genetic alterations at multiple scales (Figure 1), several of which can be modeled with networks. Genetic alterations impacting the abundance or activity of individual molecules will affect the interactions in which those molecules participate. If the affected interactions are an important component in the larger network mediating a critical biological process or cellular behavior, a disease phenotype is more likely to occur. Here, we review developments in modeling molecular interactions within the cell, how mutations impact molecular interactions and biological processes in disease phenotypes, and how this knowledge can be exploited to elucidate key genotype–phenotype relationships.

Networks for biological inference

Networks provide a framework for deriving information from a set of relationships among biological entities. In models of subcellular biological processes, network nodes are typically genes, proteins, nucleic acids or metabolites, and edges represent physical interactions or a rich variety of functional associations (Table 1). Hybrid networks that are mixtures of different types of relationships are prevalent as well.

Table 1

A summary of several common varieties of biological network and some examples.

Network type	Nodes	Edges	Example
Protein–protein interaction (PPI)	Proteins	Physical interactions	HPIN [26•]
Structurally resolved PPI	Protein	Physical interactions	HSIN [26•], SIN [58], Interactome3D [44], INstruct [45]
Protein–DNA interaction	Transcription factors	Transcription factor DNA binding	[91,92]
Co-expression	Proteins	Common expression	[93]
Genetic interaction (GI)	Genes	Common function	[18,69]
Difference	Genes	Differential function	[66]
Metabolic	Enzymes, metabolites	Biochemical reactions	[94]
Non-coding RNAs	miRNA, lincRNA, asRNA, target genes	Physical interactions, common function	[95]
Integrated	Any	Any	HumanNet [54], BioGrid [96]
Hierarchical	Any	Any	Nexo [90••]

Biological network models can be constructed from systematic genome-wide unbiased screens or focused interrogation of distinct biological functions. For complex disorders that are poorly characterized, mapping candidate genes and mutations implicated by association studies onto holistic network models can implicate underlying biological processes (Table 2). In a recent GWAS of coronary artery disease (CAD), Deloukas *et al.* identified subnetworks

Table 2

Summary of recent network-based strategies for identifying biological mechanisms underlying genetic disorders. Methods are grouped into two types: Exploratory Methods evaluate biological trends relating genotype to phenotype, while Analytic Methods seek to uncover a specific mutation, gene or biological pathway underlying a specific disorder (LoF = loss of function, PPI = protein–protein interaction, DE = differential expression, eQTL = expression quantitative trait locus).

Type	Goal	Data	Strategy	References
Exploratory	Network for analysis of disorders associated with blood vessels	Protein interactions, protein domains	GeneHits: method based on graph kernel diffusion	[16]
	Network for analysis of HIV host cell defense evasion mechanisms	Affinity-tagging purification/mass spectrometry	MiST: uses information about protein abundance, reproducibility and specificity across replicate experiments	[17]
	Explore network properties of LoF tolerant genes	Gene annotations, interactions from multiple network databases	Use custom Multinet to investigate statistical correlation between genes and network properties, fit a linear model to separate essential and LoF tolerant genes using network properties	[58]
	Explore molecular basis of genotype–phenotype relationships	Mutation databases, PPI databases	Build a PPI network with structurally resolved protein interaction interfaces for analysis of mutations in inherited diseases	[25,26•]
	Explore the relationship between network state and cellular outcome	TP53 signaling network, condition specific cellular outcome data	Build a Boolean model of simplified TP53 signaling, map model dynamics to cellular outcomes, use the model to simulate how removing genes affects cellular outcome	[28••]
	Evaluate how a network motif contributes to cell fate decisions	Cell cycle pathway, yeast response to mating pheromones	Generate hypotheses based on network structure, test experimentally and build differential equation models	[29••]
	Explore how drugs rewire biological networks	Time series gene expression, cellular response, growth factor signaling and DNA damage response pathways	Identify candidate genes from pathways or DE after drug exposure, select a subset of genes based on prior knowledge or pathway structure, use time series data for genes model signaling to cellular outcome	[31••]
	Explore how SNPs effect gene expression in different tissues	Microarray based SNP and expression measurements	Combine eQTL analysis with a sampling approach to detect tissue specific SNP effects on expression	[64•]
	Organize genetic interaction as a hierarchical network	Genetic interaction screens in yeast	A minimum description length criteria is minimized using greedy and local search methods from an initial clustering.	[67]
	Organize interaction edges in a hierarchical ontology of terms	Physical and genetic interactions, mRNA co-expression	Combine probabilistic clustering with an ontology alignment method to produce robust hierarchical structure directly from experimental measurements and networks.	[41,90••]

Table 2 (*Continued*)

Type	Goal	Data	Strategy	References
Analytic	Identify biological pathways underlying hemimegalenchephaly	*De novo* somatic mutations, pathway gene sets	Map onto canonical pathways	[8]
	Identify disease genes from *de novo* CNVs in autism cases	*De novo* CNVs, protein architecture, function, and expression, pathways	Identify genes across CNVs implicated in similar phenotypes	[19]
	Identify biological pathways underlying CAD	CAD GWAS loci, commercial network database	Identify subnetworks from GWAS implicated genes, annotate subnetworks, identify overlap with canonical pathways	[15]
	Identify genes underlying type 1 diabetes	GWAS loci, protein interaction network, gene expression	Identify subnetworks from GWAS implicated genes, map DE onto subnetworks and test for statistical enrichment of DE genes	[56]
	Identify genes underlying autism	*De novo* somatic mutations, protein interaction network	Identify connected subnetworks based on *de novo* mutated genes, functionally annotate subnetworks	[57]
	Identify genes that regulate plasma insulin levels	Genotypes, clinical traits, transcriptional, hybrid network	Identify subnetworks from eQTLs in different tissues, prioritize genes that participate in inter-subnetwork edges	[59]
	Identify cancer related genes and pathways	Gene expression data and SNP data	A set-cover based approach is used to identify subnetworks which explain an eQTL relationship between causal genes and potential targets	[81]

enriched for genes implicated by variable expression with or physical proximity to SNPs in a larger protein–protein interaction (PPI) network [15]. Subsequent gene set analysis to determine functional enrichment of the subnetworks, and analysis of subnetwork overlap with canonical pathways implicated crosstalk between lipid metabolism and inflammatory pathways as underlying the pathogenesis of CAD.

If the disease is better understood, focused models may enable development of specific biological hypotheses about the mechanisms by which alterations cause disease. For example, Chu *et al.* constructed a network of protein interactions involved in angiogenesis, which they dub 'the angiome', in order to study diseases related to irregular blood vessel formation [16]. In another example, a network of human-HIV protein complexes constructed by affinity tagging and purification mass spectrometry has provided a near-comprehensive view of how HIV evades host cell defenses [17]. While focused approaches represent only a partial view of the cell, the resulting networks provide an intelligent framework for constraining hypothesis testing to proteins most relevant to a disease. On the other hand, focused screens may miss systems level trends, for example cross-talk between biological processes, that can play a role in disease [18].

Network edges can also represent abstract relationships derived from biological knowledge. Gilman *et al.* built a network where all pairs of proteins are connected by a weighted edge representing the *a priori* expectation that the proteins participate in the same phenotype. Edge weights were based on evidence sources such as tissue-specific expression, pathway membership, common functional annotations and similar domain composition [19]. They then searched over this network to identify the most functionally similar genes affected by *de novo* copy number variants (CNVs) in autism cases.

Mutations as network perturbations

The majority of known disease mutations annotated in the Human Gene Mutation Database (HGMD) cause changes to the amino acid sequence of proteins [20]. These changes can have a spectrum of consequences ranging from completely abrogating protein activity to having no effect at all, and a variety of computational strategies have been developed to predict the functional consequences of mutation at the protein level [21–23]. Changes to a protein's activity are indirectly linked to altered cellular behaviors by the network of molecular interactions in which it participates. Thus it has been proposed that to understand genotype–phenotype relationships it will be necessary to quantify the effects of mutations on molecular networks [24].

To investigate how interaction networks mediate phenotypic effects of mutations, Zhong *et al.* experimentally profiled protein interactions for twenty-nine alleles associated with five genetic disorders [25]. This profiling suggested that mutations could have three distinct effects for the PPI network: they could eliminate all interactions, remove a subset of interactions, or have no effect on interactions. To more systematically study how mutations affect physical interaction networks, Wang *et al.* constructed a high quality PPI network with structurally resolved interaction interfaces [26•]. Using this network, they analyzed disease-associated mutations from OMIM [27] and HGMD and demonstrated enrichment for in-frame mutations such as or in-frame insertions and deletions at interaction interfaces. They also found that

mutations occurring at distinct interaction interfaces in the same protein could explain many cases where a single gene is involved in multiple disorders (i.e. pleiotropy) or in disorders with multiple distinct modes of inheritance [25,26•].

Models of how PPIs are rewired by mutations, sometimes referred to as 'network perturbation models', may present a useful strategy for functionally prioritizing candidate disease mutations and developing hypotheses about biological processes underlying pathogenesis [4,25]. These models can also be used to analyze the combined effects of multiple mutation and expression changes. For example, TP53 signaling is associated with cell cycle arrest and apoptosis in response to cell damage. Choi *et al.* used a simplified model of the TP53 signaling network to map combinatorial network perturbations to cellular outcome [28••]. They then used this model to explore how fixing the activation of specific molecules constrained the cellular behaviors available and what parts of the network could be targeted with therapeutics to force the apoptotic state. Relatedly, Doncic and Skotheim recently found that a simple three-gene motif embedded within a more complex network structure was sufficient to explain yeast cellular state decisions in response to mating pheromone, suggesting that it may not be necessary to model the full complexity of biological networks to capture molecular determinants of cellular behaviors [29••].

In addition to the effects on individual edges in the network, downstream processes in the cell may be rewired to maintain homeostasis in the face of perturbations [30]. Intriguingly, Lee *et al.* showed that deliberate perturbation of networks to achieve specific rewiring could serve as a therapeutic strategy in cancer [31••]. Triple negative breast cancer cells exposed to an EGFR inhibitor before chemotherapy showed increased sensitivity to genotoxic therapy. The timing of exposure to EGFR inhibitor greatly influenced sensitivity to subsequent chemotherapy suggesting that temporal dynamics of network rewiring are a determinant of cellular response to environment.

In studies of inherited disease, causal mutations are often buried in a list of candidate variants uncovered by sequencing of risk loci or disease exomes [32], and in cancers, the majority of detected somatic mutations are thought to be neutral 'passenger' events [33,34]. It has also been suggested that most post-translational modifications may not affect protein activity [35]. Information about protein sequence and structure provides important clues for discriminating effects of distinct alterations to proteins [21–23]. Thus integrated approaches combining protein sequence and structural information with networks may provide a powerful framework for identifying disease mutations and reasoning about their molecular mechanisms.

The biophysical mechanisms by which mutations alter protein interactions are diverse and are usually not captured in the abstractions provided by simple interaction networks [36,37]. Mutations altering protein conformation or binding affinity can contribute to disease phenotype without removing network edges [38–40]. Furthermore, highly connected proteins in the network are unlikely to interact with all partners simultaneously, as interaction interfaces often overlap [41,42]. Network representations that capture mutual exclusivity of binding may be helpful for predicting the functional consequences of mutations [37,42,43].

Structurally resolved interaction networks are becoming available for several species through databases such as Interactome3D and INstruct [44,45]. Studying candidate disease mutations in the context of these networks may provide important clues as to how mutations affect biological processes. Because of the limited availability of co-crystallization protein structures [46] strategies have been developed to predict structure at protein interfaces using homology models [26•]. Nonetheless, this type of analysis will only be possible for a subset of candidate disease mutations.

Joint study of co-evolution of amino-acid residues at protein interfaces and network structure may provide insights into which residues are essential for maintaining interactions [40,47,48]. Fridman *et al.* found that affinity-altering mutations in proliferating cell nuclear antigen (PCNA) could have more severe consequences for DNA replication and repair than mutations completely abolishing interactions [40]. Their findings suggest that even within interfaces, mutations are likely to have distinct phenotypic consequences. Thus it may be important to include manipulation of specific interactions as part of mutagenesis studies when experimentally evaluating candidate disease genes. Emerging genome engineering strategies provide exciting opportunities for experimentally characterizing domain specific effects of mutations on network activities [49].

Network properties of human disease genes

The non-random organization of biological networks suggests that their topology may encode information about how molecular interactions contribute to biological phenotypes [50]. Molecular interaction networks within the cell tend to be modular; that is, proteins related to the same biological activities often form connected modules within networks [5–7,50,51]. Goh *et al.* showed that this phenomenon extends to disease genes as well; genes implicated in the same diseases often cluster within PPI networks [52,53].

The existence of functional and disease modules within interactome networks supports a 'guilt-by-association' (GBA) strategy for identifying novel disease-associated genes [5,54]. GBA has been used to intelligently reduce the list of candidate disease genes in association studies [54,55]. Bergholdt *et al.* combined PPI network overlap with genes located at GWAS risk loci and subnetwork-based enrichment for differential expression to identify new candidate type I diabetes disease genes [56]. Identification of network modules enriched for mutation or variable expression under disease conditions can point to specific biological processes disrupted in disease. For example, analysis of the network distribution of *de novo* mutations in sporadic cases with autism spectrum disorders implicated a highly interconnected subnetwork of proteins involved in β-catenin/chromatin remodeling [57].

Goh *et al.* also investigated differences in network connectivity of three classes of genes: essential, inherited and somatic disease genes [52,53]. They reported that essential genes were more likely to have a large number of interaction partners and therefore be central in the network, while inherited disease genes generally had fewer interaction partners and were more peripheral. By contrast, somatic disease genes often looked more like essential genes. Khurana *et al.* further explored gene essentiality and selection in the context of different types of biological network (PPI, metabolic, post-translational modification, regulatory, etc.) as well as in a pooled network and found that highly connected genes are more likely to show strong signatures of selection [58]. Using topological and selection properties of genes, they built a logistic regression model capable of distinguishing essential genes from genes tolerant to loss-of-function events, suggesting that these properties could be useful for selecting candidate genes for sequencing and follow-up studies. Tu *et al.* used topological location at the interface between subnetworks with differential expression (DE) mediated by plasma-insulin associated genetic loci to implicate an Alzheimer's related gene, App, in type 2 diabetes [59].

These applications demonstrate how characteristics of biological networks such as topology and modularity can be used to prioritize candidate disease genes implicated by association studies. Inference based on network architecture may be particularly sensitive to the previously noted ascertainment biases that can affect network models; highly studied genes are more likely to have a large number of edges in the network than less frequently studied genes [4,5,18]. This is less of an issue for networks derived from systematic experimental screens [4,7,60], although technology-specific biases are suspected to exist [61].

Lessons from cross-species network analysis

Mounting evidence from both the study of model organisms [62•,63••] and GWAS [64•,65,4] suggests that much of the 'missing heritability' of genetic disease may result from genetic interactions (GIs). GI maps have been widely used to study epistatic phenomena in model organisms [29••,51,66,67] and have more recently been applied to mammalian species and human cell lines.

The most comprehensive GI networks to date have been generated from systematic screens in model organisms. For this reason, it is of interest to determine whether studies of orthologous proteins in model organisms could inform missing interactions in human networks. In a recent attempt to experimentally address this question on a systems level, two evolutionarily diverged yeast species were compared: the budding yeast *Saccharomyces cerevisiae* and the fission yeast *Saccharomyces pombe*, which are separated by an estimated 400–800 million years of evolution (an evolutionary distance greater than the divergence between humans and fish). Comparison of systematic pairwise genetic interaction screens conducted in both species [18,68,69] showed a hierarchical conservation of network modules, with highest conservation observed for interactions within protein complexes (68–70%), lower conservation of interactions within biological processes (38–58%) and lowest conservation of interactions between distinct biological processes (15–19%) [18]. In some cases, there was functional 'repurposing' of complexes between species [69].

Interestingly, although globally only a small fraction of the specific interactions between biological processes were conserved, the total number of interactions was similar, suggesting that coordination of biological processes may be a design principle in eukaryotic systems [18]. Because of the aforementioned divergence between these yeast species, Ryan *et al.* suggest that these trends will most likely pertain to other eukaryotic species as well. These studies provide compelling evidence that cross-species networks can aid our understanding of human disease proteins and the biological processes in which they participate.

A uniquely informative perspective is afforded by examining 'difference networks', which are emerging as an exciting strategy to examine the broader effects of perturbations on biological processes in the cell [30]. Difference networks can be derived from systematic mapping of interactions in cells under different conditions. In these networks, edges represent the interactions that differ between the tested conditions and can capture more dynamic effects of particular (e.g. drug) or environmental (e.g. heat) perturbations on the network [66,70].

Regulatory networks and non-coding DNA

Most GWAS-implicated risk variants occur outside of protein coding genes [71–73]. Recently it has been suggested that the majority of the genome is involved

in biochemical and regulatory activities, not just the 1.5% encoding proteins [74]. Non-coding genetic alterations, even those affecting non-coding RNA (ncRNA) sequence, are suspected to mediate phenotypic effects primarily by altering the abundance of proteins in the cell and thus perturbing PPI networks through stoichiometric effects [75–77]. Indeed, many variants detected by GWAS are located at DNA regulatory elements [78••]. An early investigation of the tissue-specific effects of genetic variants on gene expression uncovered surprisingly complex relationships, suggesting that network models may be essential for dissecting phenotypic consequences of non-coding variation [64•].

An analysis conducted as part of the Encyclopedia of DNA Elements (ENCODE) project [79] compared the genome-wide binding patterns of 119 distinct transcription and DNA binding factors (TFs) across five different cell lines [80]. These data were used to construct a hierarchical representation of transcription factor regulation onto which protein and non-coding RNA interaction data as well as post-translational modifications were integrated. The combined network suggested the existence of three tiers of transcriptional regulation with distinct properties and architectures. Kim *et al.* used an interaction network of similar composition to implicate genes and network paths capable of mediating disease-related expression changes downstream of copy number variants [81].

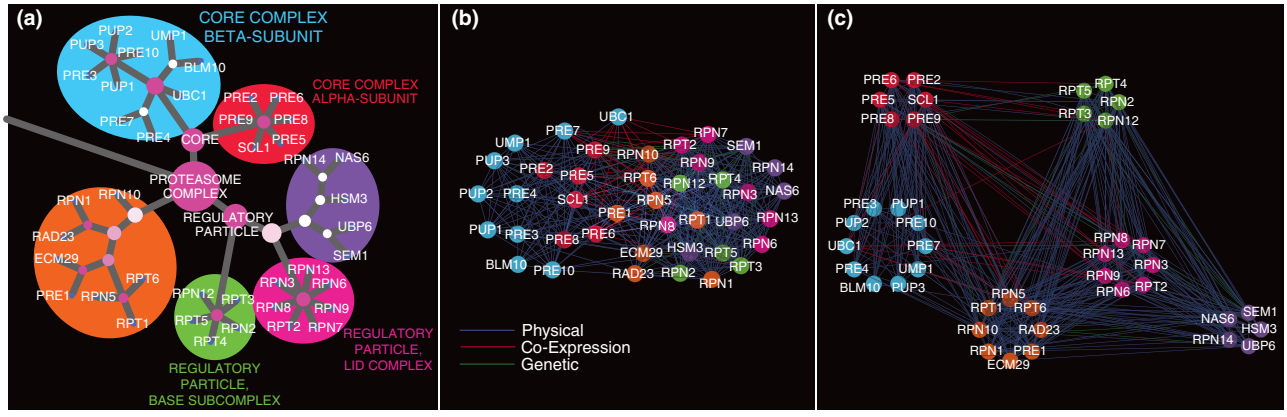
Increasing evidence points to an important role for ncRNAs in complex disorders. On the level of mutations, microRNAs (miRNAs) have been shown to play a mechanistic role in the effects of often ignored synonymous mutations [14]. A recent work has shown that a network of microRNAs may play a key role in the epithelial to mesenchymal transformation of ovarian cancers [82•]. The importance of other ncRNA species have also been highlighted, such as the role of anti-sense RNAs on PTEN regulation [83], broad epigenetic effects of HOTAIR a long intergenic ncRNA (lincRNA) in breast cancer [12], and the role of PCAT-1, another lincRNA, on the progression of prostate cancer [13].

Future challenges: context, dynamics and hierarchies

Biological network models still fall short of capturing many important aspects of biological systems. Cells exhibit dynamic responses to environmental stimuli [84] and cells of different tissue types are characterized by distinct gene expression patterns [10,64•]. These properties are key determinants of phenotype but are not captured by the standard static network models that are prevalent in the field.

Attempts to estimate the completeness and accuracy of existing protein interaction data suggest that 92% or more of binary human PPIs remain to be uncovered [3,85]. These estimates do not account for the possibility that distinct protein isoforms participate in different interactions. In addition, new molecular species are still being discovered and have not yet been incorporated into network models [7]. Constructing network models that accurately capture the molecular composition and interactions

Figure 2



Hierarchical representations provide interpretable views of how molecular networks contribute to biological function. The subnetwork comprising interactions among proteins of the *S. cerevisiae* proteasome is depicted using different network layouts: **(a)** hierarchical, **(b)** force-directed and **(c)** a layout showing within-module edges and between-module edges. In the hierarchical representation, distal nodes are included in proximal nodes (e.g. the node labeled 'core' encapsulates the alpha and beta subunits depicted in red and cyan). Node size corresponds to the number of genes participating in the term and node color gives degree of correspondence to annotated biological activities. Branches and nodes corresponding to physical complexes with known biological function are labeled. Node colors in panels (b) and (c) match the complexes highlighted in panel (a).Reproduced with permission from Dutkowski *et al.* [90••].

in specific cell types and under distinct conditions will be essential for effectively modeling genotype–phenotype relationships.

New experimental techniques are rapidly emerging that will enable systematic screens of molecular interactions in mammalian cells. Mass spectrometry (MS)-based techniques promise to enable systematic cell type-specific screens of the proteome and protein post-translational modifications [61]. Proteomics may also aid in discovery of as yet undiscovered protein coding genes [86]. Until now, the majority of GI screens have been performed in model organisms, especially yeast, by exhaustively knocking out pairs of genes and measuring the effects on colony size. Novel approaches using RNAi technologies are now enabling systematic mapping of GIs in mammalian cells [87–89].

New strategies for network construction and visualization will also aid the search for disease causing genes and mutations. Reformulating interactomes as hierarchies can provide representations of biological information that are easier to interpret than the typical 'hairball' that results when thousands of interactions are simultaneously displayed [41,90••] (Figure 2). Mapping molecular measurement data onto such hierarchies will provide novel biological hypotheses about the pathogenesis of complex inherited disease. Furthermore, the hierarchical structure can highlight inconsistent edges likely to be false positives or of lesser importance, and suggest new relationships among distinct biological complexes and processes. Aside from a few pioneering efforts, the space of hierarchical network modeling remains largely unexplored.

Conclusions

Biological networks are increasingly being applied to study the mechanisms by which genetic alterations cause phenotypic changes at the cellular level. Network organization and structure can help explain many disease phenomena such as locus heterogeneity, variable penetrance, pleiotropy, inheritance models and comorbidity. We believe these efforts are in their infancy. Limited knowledge of the dynamic and context-specific interplay of molecules within cell and our incomplete understanding of the makeup of the human genome has prevented effective modeling of the heritable contributions to human disease. Advances in experimental measurement technologies will soon enable large-scale screens to fill in much of our missing knowledge.

Conflict of interest

The authors declare no conflict of interest.

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Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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