vided by the primary physician faced with a young, distressed infant and anxious parents. Withholding therapy is much more difficult than giving it.

No potential conflict of interest relevant to this article was reported.

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Network Medicine — From Obesity to the "Diseasome"

Albert-László Barabási, Ph.D.

A recent study reported that among people who carried a single copy of the high-risk allele for the *FTO* gene, which is associated with fat mass and obesity, the risk of obesity increased by 30%. The risk of obesity increased by 67% among people who carried two alleles, and on average they gained 3.0 kg (6.6 lb) or more.[1] Given that approximately one sixth of the population of European descent is homozygous for this allele, this link between the *FTO* gene and obesity appears to be one of the strongest genotype–phenotype associations detected by modern genome-screening techniques.

That obesity has a genetic component is not surprising: researchers have long known that it often runs in families. In this issue of the *Journal*, Christakis and Fowler suggest that friends have an even more important effect on a person's risk of obesity than genes do.[2] The authors reconstructed a social network showing the ties between friends, neighbors, spouses, and family members among participants of the Framingham Heart Study, making use of the fact that the participants had been asked to name their friends to facilitate follow-up in the study. The authors observed that when two persons perceived each other as friends, if one friend became obese during a given time interval, the other friend's chances of following suit increased by 171%. Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40%. The results of this study also indicate that obesity is clustered in communities. For example, the risk that the friend of a friend of an obese person would be obese was about 20% higher in the observed network than in a random network; this effect vanished only by the fourth degree of separation.

In the past 7 years, our understanding of networks has undergone a revolution because of the emergence of a new array of theoretical tools and techniques for mapping out real networks. These advances have included some surprises indicating that most real networks in technologi-

cal, social, and biologic systems have common designs that are governed by simple and quantifiable organizing principles.[3] The growing interest in interconnectedness has brought into focus an often ignored issue: networks pervade all aspects of human health. One example of this trend involves social networks and their impact on the spread of obesity or pathogens — from influenza to the severe acute respiratory syndrome or the human immunodeficiency virus. The role of neural networks in various psychiatric and neurodegenerative diseases is another example. In fact, network analysis is poised to play the biggest role at the cellular level,[4] since most cellular components are connected to each other through intricate regulatory, metabolic, and protein–protein interactions. Because of these many functional links, the defects of various genes spread throughout the intracellular network, affecting the activity of genes that otherwise carry no defects.

To understand various disease mechanisms, it is not sufficient to know the precise list of "disease genes"; instead, we should try to map out the detailed wiring diagram of the various cellular components that are influenced by these genes and gene products. Such network-based thinking has already provided insights into the pathogenesis of several diseases. For example, a recent study suggested that 18 of the 23 genes known to be associated with ataxia are part of a highly interlinked subnetwork[5]; in another example, a reverse-engineered subnetwork indicated that the androgen-receptor gene might be used to detect the aggressiveness of primary prostate cancer.[6]

The existence of intricate molecular links between subcellular components and disease genes raises another possibility: that is, diseases may not be as independent of each other as medical practitioners currently consider them to be. For example, could a genetic origin account for the fact that obesity is a risk factor for diabetes? A quick look at the list of genes associated with these two diseases indicates that several genes, including ectoenzyme nucleotide pyrophosphate phosphodiesterase (*ENPP1*), peroxisome-proliferator–activated receptor γ (*PPAR*γ), and — more recently — *FTO*, may be implicated in both diseases. In addition to the well-known link between diabetes and obesity, the large number of genes shared by often quite distinct disorders indicates that these diseases may have common genetic origins. Human diseases, therefore, themselves form a network in which two diseases are connected if they share at least one gene.[7] In this disease network, obesity has links to seven diseases, including asthma, lipodystrophy, and glioblastoma (Fig. 1). Thus, the network concept reveals a number of surprising connections between diseases, forcing us to rethink the way in which we classify and separate them.

In the long run, networks may affect all aspects of medical research and practice.[8] Indeed, the fundamental question of where function lies within a cell is slowly shifting from a single-minded focus on genes to the understanding that behind each cellular function there is a discernible network module consisting of genes, transcription factors, RNAs, enzymes, and metabolites. This understanding forces us to view diseases as the breakdown of selected functional modules rather than as single or small groups of genes. Given the many components of such functional modules, there are different paths to disease-inducing systems failure; this explains why often many genes are linked to the same disease phenotype. Similarly, the effects of drugs are not limited to the molecules to which they directly bind; instead, these effects can spread throughout the cellular network in which they act, causing unwanted side effects. Therefore, drug side effects are inherently network phenomena.

Naturally, network-based thinking may account for the environmental and social influences on disease as well. In this context, we must understand the human interactions encompassing social and family links, proximity-based contacts, and transportation networks.[9] For example, recent advances in the study of sexual networks have led to new protocols for drug dispersion. These protocols are expected to be more efficient in combating the acquired immunodeficiency syndrome in underdeveloped countries than current protocols that are based on social need.[10]

The Human Genome Project has revolutionized gene hunting, leading to an explosion in the number of detected associations between genes and disease phenotypes. The beauty of genomewide association studies lies in their ability to quantify their own limitations. For instance, many of the newfound disease-associated genetic mutations account for only a tiny fraction of disease occurrences. There is a tendency to believe that the rest are hidden in more genes.

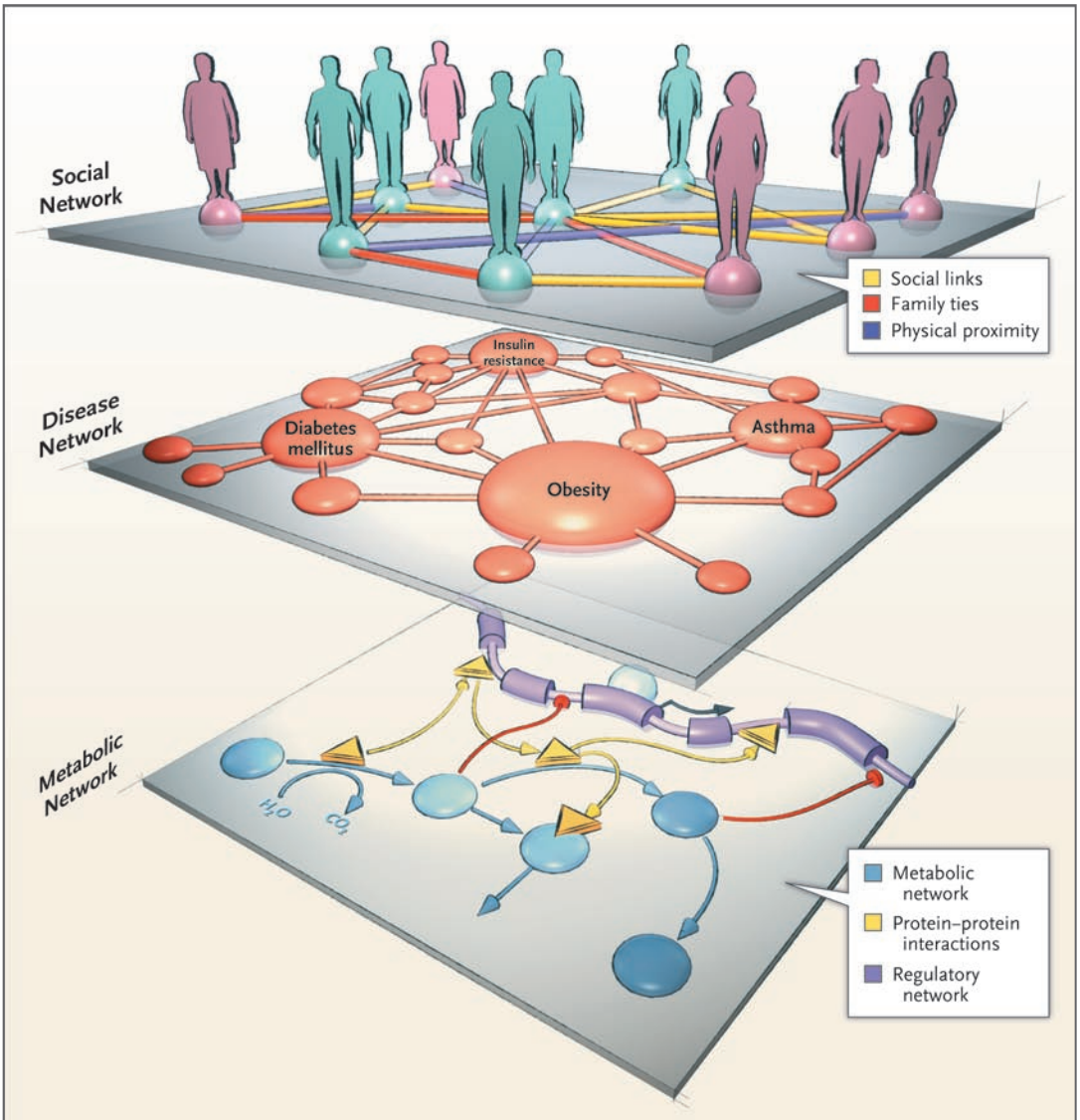

Figure 1. Complex Networks of Direct Relevance to Network Medicine.

Although they are often treated separately, most human diseases are not independent of each other. Many diseases are associated with the breakdown of functional modules that are best described as subnetworks of a complex network connecting many cellular components. Therefore, an understanding of the functionally relevant genetic, regulatory, metabolic, and protein–protein interactions in a cellular network will play an important role in understanding the pathophysiology of human diseases (bottom layer). One way to visualize the ensuing potential interrelationships among human diseases is to construct a disease network (middle layer) in which two diseases are connected if they have a common genetic or functional origin. For example, on the basis of our current knowledge of disease genes, obesity is connected to at least seven other diseases such as diabetes, asthma, and insulin resistance, since genes associated with these diseases are known to affect obesity as well. The third network of key importance to human disease is the social network, which encompasses all human-to-human interactions (e.g., familial, friendship, sexual, and proximity-based contacts) that play a role in the spread of pathogens (top layer). These networks also have an important role in the spread of obesity. Efforts to understand the interactions between the cellular, disease, and social networks are part of network medicine, which aims to quantify the complex interlinked factors that may contribute to individual diseases.

As the article by Christakis and Fowler shows,[2] the answer is not always as simple as that. Networks, in this case those that pertain to social influence, may have just as strong an impact on the development of obesity as the otherwise strong genetic effects. The role of links and connections does not stop here. In the past few years, we learned that network effects increasingly affect all aspects of biologic and medical research, from disease mechanisms to drug discovery.[3] It is only a matter of time until these advances will start to affect medical practice as well, marking the emergence of a new field that may be aptly called network medicine.

No potential conflict of interest relevant to this article was reported.

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