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NEWS AND VIEWS

Getting an edge on human disease

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It is no news that many human diseases have a genetic cause. Indeed, it is often said that you can have 'the cystic fibrosis gene' or 'the breast cancer gene'. What is meant, of course, is that we all have that gene but that people with the disease have a variant of the gene, which can cause the disease. So far, more than 50 000 disease-causing alleles, involving 1900 protein-coding genes and 2000 human disorders have been identified (Stenson *et al*, 2003). Little is known, however, about the relationships between different types of gene mutations, how they affect the corresponding proteins at a systems level, and how this relates to the manifestation of human disease.

Two broad categories of gene mutations can be considered: 'truncating alleles' that can produce a protein fragment, and 'in-frame alleles' that produce a full-length protein with a seemingly minor change in one or more amino acids. Some proteins interact with many different partners to accomplish one particular task. Other proteins can have different functions at different locations or under different conditions. Such moonlighting probably occurs due to specific interactions with different partner proteins that facilitate or prevent particular functionalities in different places or at different times. Finally, there are different manifestations of human disease: some are autosomal dominant with only one copy of the relevant gene affected, whereas others are autosomal recessive with both gene copies mutated.

In a recent article published in *Molecular Systems Biology* (Zhong *et al*, 2009), Marc Vidal and colleagues connect some of the dots between these different features by considering diseases and the mutations that cause them in the context of 'interactome' networks. Such networks are composed of proteins (nodes) and the physical interactions between them (edges). Previously, it had been observed in *C. elegans* that genetically identified mutations can affect a specific set of interactions while leaving others intact (Walhout *et al*, 2000). Such mutations are referred to as 'interaction defective alleles' (Figure 1). In the new study, this finding is extended to human interactome networks. The first observation presented is that disorders caused by in-frame alleles are often autosomal dominant: more than 20% of all autosomal dominant disorders are solely caused by in-frame alleles, whereas this is true for only ~2% of autosomal recessive disorders. Even though the effect observed is small and was revealed by careful data binning, it nicely suggests that there is a correlation between disease manifestation and different types of mutant alleles.

The authors then used an elegant interactome pipeline that is based on yeast two-hybrid (Y2H) assays. Five proteins associated with genetic disorders were selected and the interactions of the wild-type alleles with their partners were compared to the patterns of interactions observed with several of the respective disease-causing alleles. From the analysis of 29 alleles, three different interaction profiles were obtained: (1) loss of all Y2H interactions ('null' alleles), (2) loss of none of the known Y2H interactions ('pseudo-wild-type' alleles), or (3) loss of some, but not all Y2H interactions ('edgetic' alleles). These results provide further support for the notion that different interaction defective alleles result from particular disease-related mutations. As expected, mutated residues are more likely to be buried in the protein when all interactions are affected, which is likely because the protein has been rendered unstable. Conversely, edgetic mutations are more frequently surface exposed. Interestingly, however, again a correlation was observed: autosomal dominant diseases are more frequently associated with in-frame alleles that affect a surface exposed residue than autosomal recessive diseases. The authors then compared 142 genes that are associated with two or more diseases and for which at least five alleles are known. They found many genes for which the proportion of in-frame versus truncating alleles is significantly different between the diseases they cause. For 34 genes that are linked to both dominant and recessive disorders the fraction of in-frame alleles is again higher for autosomal dominant mutations. Finally, they found that genes that are involved in multiple diseases and that encode proteins with multiple domains carry mutations in different domains for different diseases, further strengthening the notion that edgetic alleles may lie at the heart of numerous human diseases.

Although the study nicely broadens our view of human genetic disease and provides an important network context, many questions remain open. For example, it will be important to determine which of the affected edges are actually causal to the disease. Furthermore, dominance might be explained by

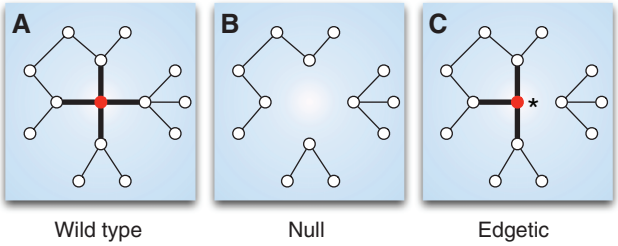

Figure 1 Node and edge perturbations by disease-causing mutations. A protein (red dot) performs its function via physical interactions (black edges) with other partner proteins (**A**). A 'null' allele results in the complete removal of the protein and thus the loss of all interactions (**B**). In contrast, 'interaction defective alleles' or 'edgetic' alleles (indicated by an asterisk) alter the profile of interactions by affecting a specific subset of edges in the interactome (**C**). Distinct network perturbations by edgetic and null alleles may cause different genetic diseases.

alternative mechanisms. *A priori*, one could imagine that gain of interactions would provide a more parsimonious explanation of dominance than interaction loss. Different alleles could confer new interactions with different proteins that result in different phenotypes. When an edge is lost it is more difficult to explain how that generally affects the function of the remaining wild type protein. It could be that, as the authors suggest, the affected protein alters a larger complex, but then how does loss of interactions with different partners give different disease phenotypes? Another potential mechanism is that mutation in protein X, results in loss of an interaction with protein Y and that this 'freed up' protein Y is actually causing the disease, even though that protein is itself not mutated.

Longer term, it will be interesting to extend the concept of 'edgetic' allele to networks of genetic interactions in order to further understand both single Mendelian disorders and complex multi-genic diseases. In addition, including other types of physical interactions in the analysis such as those between proteins and DNA will be important to understand the impact of non-coding disease-causing mutations that may affect interactions with a DNA binding protein or to study transcription factor alleles. In this context, yeast one-hybrid, rather than Y2H assays, will provide a facile tool to experimentally investigate changes in protein-DNA interactions (Deplancke *et al*, 2006). Future interactome studies that go beyond the affected nodes and its immediate neighbors, and that include different types of interactions will provide a fertile ground to reveal how subtle network perturbations cause or modulate human disease.

Conflict of interest

The author declares that she has no conflict of interest.

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