Adaptation, redundancy or resilience

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The study of the natural environment teaches us that ecological systems rich in biodiversity have greater resilience than less diverse systems, and that resource-poor ecosystems tend to have greater biodiversity to buffer against environmental change. The African savannah, a huge ecosystem, contains an abundance of grasses and other plants, herbivores and their predators. The loss of one species might be compensated for by the presence of others, but if species are relentlessly removed, one after another, the continuing loss will weaken the system until it changes its steady state and eventually collapses.

To use another illustrative example of the protection conferred by diversity: modern agriculture uses only six cereal crops as the main basic staples of the human diet. If even one crop were threatened—perhaps by a plant virus or other pathogen—the consequences for humanity would probably be catastrophic. To avoid such a scenario, breeders have created hundreds of cultivars, each with minor phenotypic changes that confer resistance to a biotic or abiotic stressor. Thus, humans too create resilience by increasing biodiversity.

In order to improve our understanding of complex diseases, we can extend this notion of diverse ecosystems to organisms. Similarly to the disappearance of one species in an ecosystem with abundant biodiversity, the loss of one gene function might not be immediately apparent, because many such changes can be compensated for, at least partly, by changes in other genes. However, a series of small, cumulative changes in many genes could lead to the breakdown of the phenotype of the organism, rendering it less resilient and more susceptible to disease, especially when it is under environmental or infectious stress. It is like throwing a stone in a pond, which generates small waves; throwing many stones at once causes a more complex

disturbance, whereby waves combine to create bigger waves or attenuate each other by interference. Thus, even inherited disorders such as hypertrophic cardiomyopathy show several phenotypes as other genes modify the action of the affected gene.

Geneticists have found many genes or whole genomic regions that have multiplied throughout the genome by duplication (Eisenstein, 2010). The repeated sequences might be identical, nearly identical or related, and they can be functional or non-functional, as is the case with pseudogenes. In terms of diversity, repeats have apparently given rise to multigene families, such as the collagens, which encode several structural proteins. Even microorganisms, such as *Mycobacterium tuberculosis*, have extended gene families or several insertions.

It was assumed previously that pseudogenes are unnecessary gene copies and therefore inactivated. Yet, there is increasing evidence that they perform a regulatory role, by influencing the function of the parent gene. The variation in copy number also seems to be as, or even more, important than the number of polymorphisms, particularly in complex diseases or phenotypic traits. One negative example is the gene that codes for glutathione transferase, *GSTM1*. Roughly half of the population carries a deletion of *GSTM1*, which reduces their ability to neutralize isothiocyanates. Clearly then, many individuals will have two null alleles and an increased risk of xenobiotic-induced disease. Another fascinating example is that preference for a high-starch diet is associated with multiple copies of the salivary amylase gene, which increases production of this enzyme.

Humans show a range of vulnerabilities to complex or infectious diseases, such as pulmonary tuberculosis. Despite an exhaustive search, no obvious, major resistance or susceptibility genes for tuberculosis have been found, although many genes—each with minor effects—have a role in disease

susceptibility. Further support for the argument that resilience comes from diversity is found in the confusion around genetic association studies in many complex diseases, in which a given gene might be significantly associated with a condition in one population, but not in others. I suspect that many of these reports can be explained by the fact that susceptibility is caused by cumulative functional changes in many genes along different routes in different groups of humans or animals. In fact, susceptibility to a common disease conferred by a single, major locus would make the organism extremely vulnerable—which is exactly what we see with autosomal-dominant inherited diseases. Thus, it is unlikely that complex diseases are caused by a solitary gene defect, as evolution would select against the high risk of a single dominant effect. Instead, we see a range of conditions and phenotypes, owing to the large number of genes involved.

This diversity of genetic factors is a blessing for humanity, as it has equipped us with enormous resilience against many common diseases, from cancer to coronary heart disease, to infectious diseases. But, it is also a bane for the geneticist and the clinical scientists who search for genetic factors that can be used to predict disease susceptibility, or the condition or progress of disease. Complexity and diversity make things far more unpredictable and messy—and therefore more difficult for scientific analysis—but both also ensure our survival against a daily assault of biotic and abiotic stressors.

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