Not too much and not too little

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The structure and function of any protein is determined by its amino acid sequence. Thus, the substitution of one amino acid for another can alter the activity of a protein or its function. Mutations—or rather, polymorphism, once they become fixed in the population—can be deleterious, such that the altered protein is no longer able to fulfil its role with potentially devastating effects on the cell. Rarely, they can improve protein function and cell performance. In either case, any changes in the amino acid sequence, whether they affect only one amino acid or larger parts of the protein, are encoded by polymorphisms in the nucleotide sequence of that protein's gene. For any given polymorphism, diploid organisms with two sets of chromosomes can therefore exist in either a heterozygous state or one of two homozygous states. When the polymorphism is rare, most individuals are homozygous for the 'wild-type' state, some individuals are heterozygous and a few are homozygous for the rare polymorphic variant. Conversely, if the polymorphism occurs in 50% of the alleles, the heterozygous state is common.

At first glance, the deleterious homozygous state seems to be something that organisms try to avoid: close relatives usually do not breed, probably to prevent the homozygous accumulation of deleterious alleles. Thus, human cultural norms, founded in our biology, actively select for heterozygosity as many civilizations and societies regard incest as a social taboo. The fields of animal husbandry and conservation biology are littered with information about the significant positive correlation between genetic diversity, evolutionary advantage and fitness [1]. In sexually reproducing organisms, heterozygosity is generally regarded as 'better' in terms of adaptability and evolutionary advantage.

Why then do we seldom, if ever, regard allelic heterozygosity as an advantage when it comes to genes linked with health and

disease? Perhaps it is because we tend to distinguish between the 'good' allele, the 'bad' allele and the 'ugly' heterozygote—since it is burdened with one 'bad' allele. Maybe this attitude is a remnant of the outdated 'one gene, one disease' model, or of the early studies on inheritable diseases that focused on monogenic or autosomal-dominant genetic disorders. Even modern genetics almost always assigns 'risk' to an allele that is associated with a health condition or disadvantaged phenotype; clearly, then, the one homozygous state must have an advantage—sometimes referred to as wild-type—but the heterozygote is often ignored altogether.

Maybe we also shun heterozygosity because it is hard to prove, beyond a few examples, that it might offer advantage. A 2010 paper published in *Cell* claimed that heterozygosity of the *lth4A* locus conveys protection against tuberculosis [2]. There is a mechanistic basis for the claim: *lth4A* encodes leukotriene A4 hydrolase, which is the final catalyst to synthesize leukotriene B4, an efficient pro-inflammatory eicosanoid. However, an extensive case-control study could not confirm the association between heterozygosity and protection against tuberculosis [3]. Therefore, many in the field dismiss the prior claim to protection conferred by the heterozygous state.

Yet, we know that most biochemical and physiological processes are highly complex systems that involve multiple, interlinked steps with extensive control and feedback mechanisms. Heterozygosity might be one strategy by which an organism maintains flexibility, as it provides more than one allele to fall back on, should conditions change. We may therefore hypothesize that heterozygosity can be either a risk or an advantage, depending on the penetrance or dominance of the alleles. Indeed, there are a few cases in which heterozygosity confers some advantage. For example, individuals who are homozygous for the CCR5 deletion polymorphism (D32/D32) are protected

against HIV1 infection, whereas CCR5/D32 heterozygotes have a slower progression to acquired immunodeficiency syndrome (AIDS). In sickle-cell anaemia, heterozygotes have a protective advantage against malaria, whereas the homozygotes either lack protection or suffer health consequences. Thus, although heterozygosity might not create a general fitness advantage, it is advantageous under certain specific conditions, namely the presence of the malaria parasite.

In most aspects of life, there are few absolutes and many shades of grey. The 'normal' range of parameters in medicine is a clear example of this: optimal functioning of the relevant physiological processes depends on levels that are 'just right'. As molecular and genetic research tackles the causes and risk factors of complex diseases, we may perhaps find more examples of how heterozygosity at the genetic level conveys health advantages in humans. As the above example regarding tuberculosis indicates, it is difficult to demonstrate any advantage of the heterozygous state. We simply need to be receptive to such possibilities, and improve and reconcile our understanding of allelic diversity and heterozygosity. Researchers working on human disease could benefit from the insights of evolutionary biologists and breeders, who are more appreciative of the heterozygous state.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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