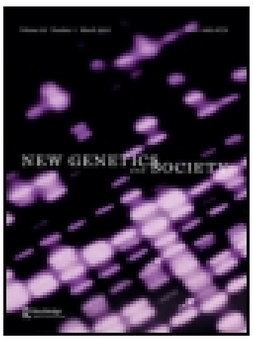

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BOOK REVIEW

A genetic unraveling: book review of *Making Sense of Genes* by Kostas Kampourakis

Despite the growing consensus among molecular biologists that individual genes cannot determine traits (i.e., phenotypes) such as intelligence, shyness, or affinity for addictive substances – or even phenotypes that were once imagined to be simple, such as eye color – many publics seem to believe that there exist "genes for" specific traits. Such beliefs reflect, in part, the circulation of this idea in a range of media and in secondary schools around the world. In an effort to dispel this dated notion, Kostas Kampourakis has written *Making Sense of Genes*, an erudite and fascinating book that presents historical and contemporary accounts of the gene concept while explaining exactly what it is that genes can and cannot do. Kampourakis clearly knows his stuff. He is not satisfied to merely make the case that genes do not determine our traits; he does the hard work of explaining how the scientists who study DNA do their work, and what they have discovered about how genes are used in the development of phenotypes.

The primary theme of *Making Sense of Genes* is that phenotype development is extraordinarily complex. Kampourakis's message could well serve as an antidote to popular forms of genetic determinism. The intended audience for this book includes "undergraduate students … as well as biology teachers and educators" (p. 9), the exact audiences that need to hear Kampourakis's lessons. Many of these readers will find the book to be accessible. Some sections contain more details than might be necessary – for example, the early chapters present a meticulous history of ideas surrounding the gene concept, and although I found these chapters to be of value, some of this history is not necessary to grasp the book's ultimate point – but Kampourakis does an excellent job of embedding basic information about the genome and its functioning into his historical narrative.

Kampourakis has a strong background studying science education, so he is well qualified to identify the sources of mistaken ideas about genetic determinism. His treatment of the public impacts of science journalism, entertainment media, and formal scientific education is enlightening, suggesting that many misunderstandings are rooted in the curricula we encounter in our schools and in the ideas conveyed in television shows and movies. Likewise, his examination of genetic testing corporations such as 23andMe is interesting and helpful; it identifies companies that are more versus less careful about their claims, and facilitates a

distinction between companies that claim to predict which health conditions a person might develop in the *future* and companies that claim to reveal a person's ancestry, thereby shedding light on their *past*.

The book's take-home message is that genes do not single-handedly determine phenotypes, but given the extensive genetic research that has been conducted in the past 100+ years, it is perhaps inevitable that a book on genes would focus on genetic contributions to phenotypes in ways that suggest they have outsized effects on phenotype development. As a consequence of his focus on genes in the middle third of his book, Kampourakis downplays in these chapters the vital interactions between organisms and their environments. This approach is, unfortunately, inherently simplifying; it glosses over the central roles of environmental factors in the development of our phenotypes. For example, where he recounts research on aggressive behavior, Kampourakis focuses on studies that concluded that specific chromosomal or genetic abnormalities might be responsible for aggressive behavior. While he discusses how these findings were misrepresented in the media, he does not attempt to debunk the idea that aggressive behavior might actually be caused by these abnormalities. He is at pains to get the minute details of the molecular biology right –

> the polymorphism consists of a repeat of 30 nucleotide pairs, present in 3, 3.5, 4, or 5 copies. The variants with 3.5 or 4 copies of the repeat were found to be transcribed up to 10 times more efficiently than those with 3 or 5 copies (p. 125)

– yet he is surprisingly credulous about the whole notion that some of these genetic variations could cause aggressive behavior on their own. Ultimately, Kampourakis writes that "further studies are required … to identify the genes underlying aggressive behavior" (p. 127), a statement that betrays his primary point that complex phenotypes are never going to be fully explained by "genes underlying" those phenotypes, because phenotypes depend on more than genes alone. He suggests that using larger samples and more homogeneous phenotypes could yield the kinds of gene-based understandings that genome-wide association studies (GWAS) attempt to generate, but this suggestion is, regrettably, overly optimistic about the GWAS research strategy, given that complex phenotypes are known to develop via co-action of genetic *and* non-genetic factors, both of which play critical roles in developmental processes.

Similarly, Kampourakis sometimes seems to accept the view that if variation in a single gene across a population is associated with variation in the emergence of a disease, then that gene can be considered the cause of the disease. Nevertheless, this sort of "translation" from population-level, correlational analyses to causal statements about individual development is never warranted. Presenting what seems to be a moderate position, he points out that

> two siblings with the same *LDL-R* alleles may have a very different phenotype because they carry different *PCSK9* alleles … it is thus clear that there is no single

> 'gene for' familial hypercholesterolemia, and more than one gene should be taken into account for disease risk estimation. (pp. 137–138)

Even so, this still leaves open the possibility that the disease phenotype in question – namely atherosclerosis (i.e., blocked arteries and an increased risk of heart attack or stroke) – might ultimately be found to be strictly genetic, if only we could identify all of the relevant genes. A similar approach is adopted when discussing cancer. However, this perspective minimizes the fact that lifestyle factors play crucial roles in the development of both atherosclerosis and cancer. Geneticists can do genome-wide association studies until they are blue in the face, but they are not going to truly comprehend the development of atherosclerosis or cancer until they have also factored in variables such as diet, exercise, and tobacco use. Given his desire to critique standard ways of thinking about genes, Kampourakis makes it hard on himself by accepting some of the conclusions of standard genetic studies (such as GWAS studies), conclusions that most critics who share his perspective find controversial.

Perhaps the most significant shortcoming of *Making Sense of Genes* is its inconsistent level of explanation. In many cases, basic information is presented in adequate detail, allowing readers with little exposure to the genetic sciences to understand the proceedings. In other cases, though, relatively complex information is presented, sometimes with very high levels of detail that might be difficult for less experienced readers to digest. For example, consider this sentence: "Reprogramming of mouse embryonic fibroblasts to iPS cells requires a mesenchymal-to-epithelial transition, i.e. a process during which motile mesenchymal cells are converted to polarized epithelial cells" (pp. 226–227). This is not a unique example; there are numerous places in the book where the intended audience of non-experts will be lost if they are not already familiar with the processes being described. As a result, although the book should be of interest to a wide swath of readers, some will find parts of the text to be simplistic while others will find parts of it to be quite challenging. Given the scales of the ideas Kampourakis is trying to convey in this book – from the molecular to the behavioral to the philosophical – maybe this sort of problem was unavoidable; after all, molecular biology is complex, and simplification can produce the very problems the author is endeavoring to address.

Happily, Kampourakis hits his stride in the last 5 chapters of the book, doing an exceptionally good job of overcoming earlier missteps. In these chapters, in which he conveys what genes truly do, he takes on meaningful issues like the difference between causality and correlation, teaching readers that correlational methods like GWAS are unable to identify genes that contribute directly to phenotypes. He also discusses oft-overlooked problems inherent in "gene-knockout" studies, problems that arise because genes are related to phenotypes in a "many-to-many" rather than in a "one-to-one" fashion.

Chapter 9 is particularly strong, conveying the significance of development and how it works. I appreciated Kampourakis's explanation here of reaction norms, and his presentation of examples showing how single genes can *appear as if* they

determine outcomes even if their effects are actually entirely indirect. His discussion of robustness and plasticity in this chapter is especially good. Likewise, his subsequent treatment of heritability – a treatment that clearly delineates the distinction between factors that cause individual traits versus factors that account for variations in traits across a population – is admirable and useful.

In Chapter 11, Kampourakis does well by his readers, bringing them up to date on recent findings about the genome, including discussions on "junk" DNA, regulatory RNAs, and the relatively new subdiscipline of epigenetics. I was pleased to see him employ Waddington's "epigenetic landscape" as an illustration, because that illustration does the necessary work of conceptually connecting epigenetic modifications with all-important developmental processes. Many modern writers discuss epigenetics in ways that lose sight of these processes, but Kampourakis has masterfully avoided this pitfall.

Finally, Kampourakis examines the practical consequences of research in molecular biology. He is appropriately skeptical of "genomic medicine" and distinguishes it from "personalized medicine," the latter being an approach that brings a much broader conceptual framework to bear on medical problems and that is therefore likely to be more effective in the long run. His dissection of the statistics associated with various alleles and breast cancers is illuminating and of substantial value, and his discussion of the likelihoods and consequences of false-negative and false-positive genetic tests was also meritorious.

The book culminates with a review that should be required reading for any individual who wants to communicate information about genes to the general public. Scientists, teachers, and journalists alike need to be particularly careful about how they use metaphors when discussing genes, as these can easily mislead people. In summing up his investigations, Kampourakis advises readers to remain "aware of current abilities and make sure not to distort them … [To date,] we can sequence genomes and we can find associations between DNA variants and characters or disease. Nothing more" (p. 249). And here he is correct: the associations we find cannot be used to predict outcomes with anything approaching certainty. His conclusion is that "Genes are not our essences, they do not determine who we are, and they are not the explanation of who we are and what we do … we are not prisoners of any genetic fate" (p. 260). Therefore, it is "time to reconsider our conception of how we come to be as we are, and to think of developmental processes as the important factors in this process instead of genes alone … Genes do nothing on their own" (pp. 252–260). In ending on this strong note, Kampourakis fulfills his promise to make sense of genes.

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