

Are We Listening to Genomic Noise?

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Sheldon Krimsky and Jeremy Gruber, eds., *Genetic Explanations: Sense and Nonsense*. Cambridge, MA: Harvard University Press, 2013, 384 pp., \$45 (hardcover).

BUZZING AROUND US is the promise of a clear understanding of life through the study of genes and DNA sequence. The buzz can be found in media reports and scientific journals alike. We are searching for genes for intelligence and longevity, and trying to decipher the links between DNA sequence, genes, and disease. A milestone in this effort was the Human Genome Project, which mapped every letter in the human genome and paved the way for the genomic era with increased access to DNA sequence information in all organisms. The view that DNA sequence contains all of the information we need to understand ourselves has seeped into our consciousness. However, a careful look at what we have learned from genomic research since the release of the initial human genome in the year 2000 reveals that genes and DNA sequences do not explain or determine many of the traits that are known to be heritable, such as height, at our current level of understanding. It may be true that ever increased resolution of individual genomes will unveil how DNA sequence feeds into multifactorial characters, but it may also be correct that DNA sequence will never be sufficient to describe most characteristics or diseases.

Through a series of essays, the book “Genetic Explanations: Sense and Nonsense” asks its readers to take pause and consider what we mean when we talk about genes. It asks whether genes as discrete, definable regions of DNA even exist in an organismal context; what we stand to learn by studying complete genomic sequences; and whether focusing on DNA sequence is an appropriate use of resources when DNA sequence cannot explain psychological states, developmental processes, or even most diseases. The conversation in the book is an important and oft overlooked one. It is easy to take for granted both the word gene and the reductionist paradigm that by studying DNA sequence, we will be able to better understand human development and disease. Here is all this information, it must explain us. “Genetic Explanations: Sense and Nonsense” argues that DNA sequence does not.

The book makes its case by evaluating the use of DNA sequence and genetics to explain phenomena in a broad

spectrum of disciplines from molecular biology to evolution, psychology, and human health. It is organized into three sections, the first of which focuses on the molecular basis of genes, what genes are and are not, and how much information can be extrapolated from genetic knowledge to explain molecular processes. The second section focuses on genetics in human health with chapters on predicting disease, DNA changes in cancer, genes in psychology and autism, and genomic medicine. The final section begins with a fascinating section on the persistence of failed scientific ideas in the public consciousness, and is generally focused on the social ramifications of promoting a view in which, DNA sequence defines us. This includes discussions on the influence of direct to consumer DNA products such as personalized genomes and family history trees, the perceived infallibility of DNA evidence in criminal cases, and the influence of a nurturing environment on behavior independent of genetic background.

The language varies greatly from chapter to chapter. Some chapters require only a basic familiarity with the concepts of genes, genetics, and genomes. In other chapters, however, a working knowledge of basic molecular biology terms and processes (DNA replication, transcription, translation, and protein) would be essential. For example, this passage from chapter six illustrates some of the technical language employed by a number of the authors: “Transcriptional states are induced and are actively maintained through interactions between small, transmissible RNA molecules and the mRNAs or the DNA/chromatin regions with which they pair.” Taken as a whole, this book would best serve readers with a fairly strong background in molecular biology and genetics such as individuals who have had college level exposure to biology.

Each chapter is written within a framework, where genes and DNA sequence are not sufficient to explain the subject at hand. Some chapters present this framework through balanced arguments, while other chapters dedicate the majority of their space to exposition. In early chapters, the authors argue that collections of genes or sequence variants will never be sufficient to explain the majority of evolutionary change, physical traits, or disease:

“The recognition that phenotypes are inherited via non-linear, plastic, orthogenic developmental mechanisms, and not simply by collections of genes, implies that some of the major conclusions of the modern [evolutionary] synthesis must be incorrect.”[Chapter2, pg 29].

"But it turns out that the Mendelian conception of genes not only fails to capture accurately what determines our eye colors; it actually fails to represent accurately how genes contribute to any of our traits. In fact, it is no longer even clear that there really are such things as Mendelian genes contained in our DNA that determine the final forms of our biological or psychological traits." [Chapter 4, pg 46].

"What occurs inside any individual cell in a tumor is thus a consequence of that altered communication within and among tissues. Although the tissue organization field theory (TOFT) acknowledges that mutations might be generated throughout the carcinogenesis process, they appear irrelevant to carcinogenesis and its progression." [Chapter 7, pg 91].

The above statements are thought provoking and well supported in their respective chapters. The ideas are important and interesting counterpoints to notions of evolution mediated by variation in DNA sequence, inheritance of traits by the passing down of genes, and carcinogenesis via acquired mutations in single cells.

The book is critical of the human genome project and genomic research in general, echoing the sentiment that the promises of the human genome project have not been fulfilled, particularly with respect to impacts on human health:

"The project to map the genetic predisposition to disease was the main rationale for the \$3 billion Human Genome Project that, decades later, has delivered next to nothing, basically because it is not genomic DNA but epigenetic environmental influences that overwhelmingly affect our health and well-being." [Chapter 16, pg 260].

Strong statements, like the one in the above quote, are scattered throughout the book. They reflect the focus of the book—to provide a general counterpoint to DNA sequence-based research across several fields. The authors occasionally overlook, however, the indirect benefits of past and current genomic research. The field that Chapter 16 is focused on, epigenetics, for example, has benefited greatly from the information gleaned from and technology developed for genomic research. The chapter goes on to cite several studies on the effect of maternal care on promoter methylation patterns and gene expression that include whole genome or transcriptome analysis, which would not have been possible were it not for the technical and informatics advances of the Human Genome Project. So, while DNA sequence does not seem to directly influence the epigenetic changes under discussion, information garnered from studying nucleotide sequences was used to support the findings.

The chapters largely present well-reasoned arguments that draw attention to the limitations of genetics and DNA se-

quence in explaining phenomena in the field at hand. It is on this matter that the book succeeds enormously. "Genetic Explanations: Sense and Nonsense" assembles evidence and testimony that we are more than the sum of our parts; that our DNA sequence does not determine or limit our potential mentally or physically because as living organisms, we are plastic, stochastic, and adaptable. An interesting way to view DNA in light of the book's polemic is mentioned in two separate chapters that describe DNA as a *resource* in a cell that allows the cell to function, rather than as a set of instructions to build a cell.

Regardless of whether you believe that genomics is the wave of the future or think that it has only revealed the limitations of DNA sequence, this book provides a fascinating and important set of arguments to ponder. It provides a sobering look at the genomics revolution, showing the continuously expanding genomics research paradigm in an unfavorable light. It is a worthwhile read for anyone interested in genetics because it presents a point of view not typically encountered that will enable readers to tune out the buzz and think critically about the meaning of the word gene and the utility of genomics. We want to be able to make sense out of this growing mass of information, and it seems that as we get a more complete picture of our population in larger and larger studies, eventually all those sequences must add up to something; however, the data up until now suggest that even a complete picture of every nucleotide in existence will provide no certainties. Biology is probabilistic by nature and the multiple actions, interactions, and reactions occurring continuously within an organism are not likely to be written into the DNA code in any meaningful deterministic way (hence, DNA as a resource rather than an instruction). "Genetic Explanations: Sense and Nonsense" invites its readers to be critical of genomic research and consider alternative research paradigms that rely less on sequencing and informatics and more on understanding genetic and developmental plasticity.

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