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BOOK REVIEW

Genetics in Context

Haskel-Ittah, M., & Yarden, A. (2022). Putting Genetics in Context: Implications for Instruction, Understanding, and Beliefs. Springer Nature Switzerland. ISBN: 9783030860509. 177 pages. Price: £99 (Hardcover)

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The mechanisms that underlie heredity are complex and abstract, a fact not lost on parents, children, teachers, or the authors and editors of the ten chapters in "Genetics Education for the 21st Century." The book spans a range of topics, including how best to introduce concepts related to hereditary mechanisms (DNA first, Mendel first, or Mendel not at all), and issues related to learning progressions and student reasoning about "traits" and the complexities of genotype-phenotype relationships, influenced by genetic background effects, environmental factors, molecular level noise, and mutations.[1] There are chapters on the impact of how the presentation of hereditary mechanisms influences the development of genetic "literacy" as well as "essentialist" and "deterministic" habits of mind that can impact students' views on topics as diverse as eugenics, population (miscast as "racial") differences, and racist and sexist prejudices. A major focus is the prevalence of deterministic and essentialist thinking, the complexities of genetic processes, and how students' understanding may be influenced by teachers' pedagogical choices, including the introduction of research experiences. There is even a chapter that appears to argue that educators should, in the cause of "social justice, " consider students' hereditary predispositions, based on what appears to be the assumption that intelligence maps onto a single linear dimension, independent of socio-environmental influences. This assumption seems to me to be misguided, at least until more effective curricular design and learning outcomes measures have been established. Moreover, there are good reasons to doubt whether simple links between genotype and complex phenotypes, such as learning ability and motivation,

[1] I find myself using lots of "scare quotes" because often the definitions of words are unambiguously and explicitly stated.

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can be established (see Fletcher, Wu & Lu. 2021. Polygenic Screening: What's the use? *Elife*, *10*, e73193).[2]

1 What Should Students End Up Knowing?

All of this raises an over-arching concern that applies to many of these otherwise valuable contributions—the authors offer very little explicit discussion as to what, exactly, a reasonable understanding of the molecular, cellular, developmental, environmental, ecological, and historical bases of hereditary processes looks like and how they can be objectively and meaningfully assessed at a particular grade level. What characteristics, exactly, does a genetically literate person display or possess? What do they need to know and what does that knowledge enable them to do? Should they be able to critique arguments on "racial" differences in "intelligence" or identify the flaws in a news story, press release, YouTube video, or Facebook/Twitter post? The genetic diversity of African populations is a case in point; do they know, for example, how many distinct populations have been arbitrarily lumped together into a single "race" (Tucci & Akey 2019. The long walk to African genomics. *Genome Biology* 20:1-3)? As noted by Donovan and colleagues (2019. Toward a more humane genetics education *Science Education* 103: 529-560), do they appreciate the extent to which members of different populations share a common history, as well as alleles that reflect common environmental (selective) factors, such as endemic malaria or solar exposure? Do students appreciate the average effect size of a particular allele or how genetic background (the other alleles present in the genome) can influence the effect of an allele on phenotype, the number of genes that influence most traits, or the complexity of mutational effects and mechanisms (see as examples, Melamed et al. 2022. De novo mutation rates at the single-mutation resolution in a human HBB gene-region associated with adaptation and genetic disease. Genome Research. https://doi.org/10.1101/gr.276103.121 and Veitia 2022. Who ever thought genetic mutations were random? *Trends in Plant Science.* https://doi.org/10.1016/j.tplants.2022.03.003*)? In sum, do they have the critical chops and necessary knowledge to identify genetic bullshit (Frankfurt & Bischoff 2005. On bullshit*: Cambridge Univ Press) when they come across it?

2 Authors and Chapter Titles

- Chapter 1: Kampourakis—an argument for a Mendel-free biology
- Chapter 2: Castro-Faix and Duncan—learning progressions for genetic literacy
- Chapter 3: Haskel-Ittain—reasoning about the (complex) gene-trait connection
- Chapter 4: Gericke—epigenetics and understanding the nature/nurture distinction
- Chapter 5: Dorfman and Yarden—do "authentic" scientific experiences aim in understanding genetics
- Chapter 6: Gericke, El-Hani, Nehm, and Menezes—the prevalence of genetic determinism
- Chapter 7: Stern, Kampouakis, Delaval, and Muller—how non-scientific attitudes shape understanding genetics

[2] In any case, something as "simple" as height is genetically complex, with associations between height and body shape, and influenced by hundreds to thousands of genes. see: https://www.sciencemag.org/news/2020/11/landmark-study-resolves-major-mystery-how-genes-govern-human-height. Surely intelligence (assuming it is one thing) is as complex.

- Chapter 8: Hammann, Heeman, and Zang—the educational challenge of genetic complexity
- Chapter 9: Donovan, Salazar, and Weindling—making genetics education more "humane"
- Chapter 10: Reiss—genetics and social justice

At its root, the problem is that often how students are introduced to hereditary processes is either a cartoonish over-simplification or is obscured by irrelevant molecular details. With regard to Mendel, Kampourakis explicitly makes this point.

> "Weldon's studies of varieties of pea hybrids led him to conclude that there was a continuum of colors from greenish yellow to yellowish green, as well as a continuum of shapes from smooth to wrinkled. It thus appeared that in obtaining pure-bred plants for his experiments, Mendel had actually eliminated all natural variation in peas, and that characteristics were not as discontinuous as he had assumed."

The idea that a particular trait is dichotomous (either/or) and determined by one or the other allelic version of a gene underlies the premise of genetic determinism, yet as noted by one of the founders of modern genetics "(f)ailure to realize the importance of these two points, namely, that a single factor may have several effects, and that a single character may depend on many factors, has led to much confusion" (Kampourakis quoting Morgan et al 1915). Does a focus on simple dichotomous traits and Punnett squares obscure the fact that chromosomal regions, consisting of the allelic variants of multiple genes, are typically inherited together? Are students able to recognize the impact of genetic linkage and background effects on the genotype-phenotype relationship, the extent and degree to which a trait is manifest, or how wrinkled, exactly, a particular pea is? Acknowledging this complexity moves the focus away from simple genetic determinism.

Something similar occurs when instruction is "anchored" in a molecular approach. What details, exactly, are important for developing a molecular understanding of hereditary processes? What types of tasks will students be expected to perform with such knowledge? Does it matter, for most students and most tasks, whether the product encoded for by a gene is a polypeptide or a non-coding RNA? If students are expected to memorize the "parts" of a gene and the multiple processes that interact to regulate gene expression and functional outcomes, is it because they will be asked to use that knowledge to make plausible predictions on how specific mutations or allelic variants could influence outcomes or phenotypes (something that specialists can rarely do accurately)? In the absence of explicit examples of desired learning outcomes, the reader is left to imagine what students can do with what they "know" beyond recognizing or regurgitating it—a situation that can make evaluating the impact of various educational strategies difficult.

The situation also applies to educational interventions that emphasize the levels of variation between individuals within a population, in contrast to the overwhelming similarities between populations (see Donovan et al 2019. Toward a more humane genetics education: Learning about the social and quantitative complexities of human genetic variation research could reduce racial bias in adolescent and adult populations. *Science Education*, 103: 529-560). The challenge is in balancing population level arguments with observations, such as those by Green et al (2010. A draft sequence of the Neanderthal genome. *Science*, *328*:710-722) who reported that Neanderthals and the hypothetical chimpanzee-like ancestor of humans and Neanderthals differ by "78 nucleotide substitutions that change the protein-coding capacity of genes where modern humans are fixed for a derived state and where Neandertals carry the ancestral (chimpanzee-like) state." This leads me to point out the general

lack of discussion about the interplay between genetic/hereditary/molecular and evolutionary mechanisms. Stern et al. consider the importance of introducing students to the ubiquity of mutation as a counter to essentialist (unchanging) views on genes but exactly how students come to appreciate the fact that DNA is not inherently stable and that mutations that appear can either persist or be eliminated at the cellular or organismic level based on their impacts on survival or reproductive success is not clearly presented. Introducing students to the work of Luria and Delbruck (1943. Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* 28: 491), that implied that mutations appear at random rather than being induced, together with recent, and highly visual work, such as the "megaplate" studies on the appearance of antibiotic resistant bacteria (Baym et al., 2016. Spatiotemporal microbial evolution on antibiotic landscapes. *Science* 353:1147-1151) could help students develop a better understanding of the origins of allelic variation and provide a background for evaluating the impact of more "hands-on" experimental studies, as described by Dorfman and Yarden. Similarly, considering the "birth and death" of genes over time might help dispel strict essentialist thinking. In this light, the original point of the "Central Dogma" proposed by Crick (1970. Central dogma of molecular biology. *Nature* 227, 561-563) is often misinterpreted; it was not meant to describe (and justify memorizing) the mechanisms of gene expression, but rather the assertion that information flows out of the gene, not into it that mutation and selection are the source of genomic information—an insight relevant to understanding where new genes and the allelic variations between different populations come from (see Blevins et al., 2021. Uncovering de novo gene birth in yeast using deep transcriptomics. *Nature communications*, *12*, 1-13). In the age of single cell gene expression analyses, we have come to recognize that a large "non-gene" fraction of the genome serves as a template for RNA synthesis, and that "regulatory noise" can, on occasion, be captured to form new genes. This has important implications for understanding evolutionary processes.

3 Genetic Education's Impact on Bias

A major concern of many of the *Genetics Education* authors is the impact of genetics instruction on students' views on genetic determinism and essentialism, views that can bolster support for, or acceptance of, sex- and "race"-base prejudices. An underlying reality that *Genetic Education* leaves largely undiscussed is that biological systems display both essentialist and deterministic features, together with recognizable variation between individuals. After all, cats are like but not identical to other cats, and differ from lions, pangolins, and peas; differences that arise from genomic differences. While there is an underlying continuity of life, the river of life has been undergoing repeated branching events leading to the formation of phenotypically distinct populations, shaped by various forms of selection, together with historic and stochastic processes (i.e., founder and bottleneck effects and genetic drift). An organism's traits are dependent on the genome present. Domesticated dogs are dogs, and apparently derived from an ancestral population distinct from that that led to wolves (Bergström et al., 2020. Origins and genetic legacy of prehistoric dogs. *Science* 370: 557-564). Quantifiable genomic differences underlie the differences between wolves and dogs. While distinct from a strict essentialist view, based on independent creation events (after all dogs and wolves do share an earlier common ancestor), these differences are real and significant. The differences that generate phenotypic differences are not imposed on members of the population, but are built through changes in DNA sequence that accumulate over evolutionary time and are influenced, in turn, by environmental, historic, and behavioral factors

(Jablonka & Lamb, 2005. Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic variation in the history of life. Cambridge: MIT press).

While genes are often seen as the sole drivers of these processes and the targets of variation, there is a deeper biological reality in play. A fact often overlooked, particularly at the introductory level, is that genes, in and of themselves, mean nothing outside of the context of a biological system, whether a cell or an organism. The cellular environment determines what a gene product "means;" whether the gene is expressed (are RNA polymerases recruited leading to the synthesis of RNA molecules) and how the gene product influences the system, including gene expression. Newly synthesized RNAs may encode polypeptides or they may act in a number of other ways, including influencing various aspects of gene expression. A gene, and the molecules it encodes, do not act *in vacuo* but are part of a dynamic interaction network, characterized by various forms of feedback, emergent, and adaptive responses. The history of the cell (organism), as well as stochastic processes inevitable at the molecular level, combines to produce epigenetic effects that can persist through cell division and that influence which genes are expressed, the molecular interactions that occur and their effects that underlie various processes and lead to specific phenotypic effects. As an example, metabolic changes can lead to unexpected modifications of histones, that in turn can alter the accessibility and expression of genes (see Gabor, Glastad & Berger, 2020. Food for thought. *Science* 370: 660-662). The network of interactions involved in producing even the simplest of traits influences the impact of any particular allele, so the question is does a specific course design and instructional strategy lead to students who understand, and can explain how allelic differences can influence the molecular, cellular, and organismic behaviors that produce "traits" and influence phenotypes?

4 Shaping Instruction and Outcomes

The first question we need to answer when designing effective instructional strategies is what exactly do we want students to be able to do after instruction? Is it to be able to develop a critical analysis of racist/sexist genetic claims, to evaluate the genetic bases for personalized medicine or the probability of getting a disease based on a genetic analysis, or a clear view of what predictions of ancestry actually mean? And what would such critical analyses look like, what ideas and facts would it rely on and build upon? I would suggest that this means we need to avoid presenting over-simplified "just so" stories, whether Mendelian or molecular. If we present Mendel's traits, we need to acknowledge how his studies were simplified through the removal of genetic background and gene linkage effects. We might consider blood type, among the most Mendelian of human traits, and its molecular basis as a useful exemplar of a discontinuous trait. We might also place essentialism in context by considering how the frequency of blood types in various populations does not track with "racial" categories.[3] To avoid "naive" determinism, we might be more explicit about the impacts of internal and external environments, focusing on how environmental factors can alter phenotypic outcomes: extreme nutritional effects and fetal alcohol syndrome are obvious examples. We might consider how various experiences and behaviors, such as acute stressors leading to post-traumatic stress disorder (PTSD), the impact of exercise on neural function, and the effects of toxins and mutagens (lead contamination of drinking water springs to mind) can influence phenotype. These are concrete examples that

[3] Distribution of blood types: https://www2.palomar.edu/anthro/vary/vary_3.htm

can be linked to genomic and epigenetic modifications. Discussions of the expressivity and penetrance of allele-associated phenotypes would seem appropriate to reinforce the idea that carrying a particular allele is generally not deterministic. Considering the independent segregation of maternal and paternal chromosomes and recombination events during meiosis seems essential to understanding relationships between parents and offspring, as well as phenotypic variation. The molecular details of these processes, however, may be more of a distraction. When considering the presentation of molecular mechanisms, we need to avoid memorization for its own sake (what might be called the illusion of rigor) and focus on what such information enables students to do—can it help them make plausible predictions as to the effects of specific mutations, alleles, or environmental factors? Can they recognize how genetic background may alter an allele's phenotypic effects (see Sittig et al, 2016. Genetic background limits generalizability of genotype-phenotype relationships. *Neuron* 9: 1253-1259 and Mullis et al., 2018. The complex underpinnings of genetic background effects. *Nature communications* 9: 1-10). After all, this is one of the major lessons of experimental studies, and why studies in inbred model organisms are often problematic when applied to humans.

While the various contributions provide a number of valuable insights into genetics education, many fall short for me because of the general lack of focus on exactly what desired learning outcomes look like. Being more specific, identifying core challenges and goals, will help instructors and researchers focus on productive strategies and increase the likelihood that improvements in course design will lead to a meaningful increase in students' working knowledge and critical understanding of the complexities of hereditary mechanisms; an understanding that will become increasingly important in helping them evaluate the growing flood of genetic information and misinformation they are likely to encounter.