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Book Review

Blueprint

Robert Plomin Allen Lane (2018), 288 pp., ISBN: 9780241282076

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In *Blueprint*, Robert Plomin tells us how a series of discoveries over the past 30 years has led to the formulation of polygenic risk scores, which are compound genetic biomarkers that correlate with continuously varying traits. Each polygenic risk score is generated from (tens of) thousands of single nucleotide polymorphisms (SNP) variants, each shown to associate with specific traits within a population. In short, polygenic risk scores are a new way of using population data for individual risk estimation.

Before polygenic risk scores, it was impossible to estimate an individual's risk for a particular complex trait based on their genetics alone, as each SNP accounts for less than half of 1% of variation in that trait. Although in their infancy, polygenic risk scores have shown initial promise in estimating disease risk because their variation accounts for a much higher percentage of trait variation. Examples are provided for body mass index (4% of variation), height (17%), intelligence (4%), the 'quantitative liability' for schizophrenia (7%) and Alzheimer's disease (5%), although these figures are still rising. However, these proportions still represent the minority of the total genetic contribution to variation.

As a part of the recent history of the genetics of complex traits, Plomin tells us about his own contributions to the field, through his use of adoption and twin modeling approaches, and discusses some of his own polygenic risk scores. The twin dimension is pertinent, because it enables him to discuss two major analytical models: heritability (the proportion of phenotypic variance due to genetic variation) and variance component decomposition (phenotypic variance partitioned into genetic, shared and non-shared environment). Importantly, both depend on age and population, and the latter leads to discussions on blurring the distinctions between genes and environment. Although these models provide depth to the arguments Plomin presents throughout his book, there are key points in his arguments that require further attention.

First, when Plomin talks about the distinctions between genes and environment, gene–environment interactions, he provides examples that reflect current ideas around the role of nature and nurture. Some of these include: 'we select, modify and create environment correlated with our genetic propensities' (gene–environment correlation); genetics can influence our perception of environment (gene–environment interaction); and an adult's genetic constitution can react to their offspring's genetic constitution (he calls this 'the nature of nurture'). While these relationships are all plausible and supported by some evidence, the amount of time Plomin spends illustrating these points seem at odds with statements such as 'nature and nurture can be disentangled' (p. viii).

Plomin also reiterates the notion that the results from some genetic risk scores are compatible with the idea that many traits are 'just extremes of quantitative dimensions'. One example provided is the two extremes of reading ability and disability, which would lie at the opposite ends of the same genetic risk score. The idea of quantitative dimensions is also compatible with finding that neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder share quantitative traits and common genes (Rommelse et al., 2010). This implies that studying individual phenotypic dimensions may, for some disorders, be more productive in discovering genetic etiologies and addressing the needs of an affected individual than studying categorical diagnoses. Clearly, more investigation is required to further test such ideas.

The book also highlights how traditional twin models may not be ideal in all situations—a clear example is how he deals with heritability. While acknowledging the above definition, there is at times a little too much reliance on specific estimates, which ignores the impact of large differences in non-genetic components of variation. For example, the difference between developed and developing countries is likely to be due to large differences in environmental factors such as sanitation, war and social policy, which cannot be ignored. Plomin acknowledges that 'rare events like abuse' would contribute to phenotype; however, we know that 1 in 12 women and 1 in 25 men have reported severe psychological abuse in childhood (Afifi et al., 2012) and that 1 in 3 women and 1 in 4 men have been in abusive relationships as adults (Young, 2015). Therefore, the effect of this type of 'extreme' environment is likely to be widespread. In addition, as we know that almost all traits have a genetic component, it is not helpful to say that a particular trait is simply 'heritable' (p. 5), as it prevents more nuanced conversations about what may (or may not) contribute to phenotypic variability.

A major strength of this book is that one of its main take-home messages is that genetics contributes to all our traits and behaviors. In some places, Plomin goes a step further and notes that genetics can even contribute to factors that are traditionally thought of as 100% environment, such as how we nurture our children and socioeconomic status; for example, Plomin's 'the nature of nurture' explanation of how an adult's genetic constitution reacts to their offspring's genetic constitution. He also explains why our reaction to specific environments has a genetic component. Both are plausible and supported by some evidence. However, it is controversial to state that the purported genetic contribution to socioeconomic status may be in part due to a genetic influence that leads some to seek out specific environments. Plomin notes that this may be in part due to the genetic contribution to intelligence, which is correlated with socioeconomic status. He states that 'we differ in propensities to experience life events and social support' (p. 90). This is one instance where he might be better situated to critically evaluate the evidence that currently exists, instead of extrapolating and predicting what the limited evidence might mean.

Problematically, Plomin frames the genetic contribution to trait variation in a deterministic manner by his use of the words 'blueprint' and 'predictor' throughout the book and in phrases such as 'fortune teller'. This alone adheres to others' use of metaphor; however, in places he adds in uncertainty using phrases such as 'genetics

is not a puppeteer pulling our strings' and 'genetic influences are probabilistic propensities not predetermined programming' (p. 43); 'polygenic risk scores will always be probabilistic, not deterministic' (p. 150); and 'heritability describes what *is* but does not predict what *could be*' (p. 91). In these places, Plomin is, unwittingly, acting as his own critic. By glancing at the plots of trait variation on polygenic risk scores for that trait – for example, for height (p. 142)—one can see that for most polygenic risk scores, the confidence intervals of phenotypes are very broad. In agreement with this inaccuracy, some of Plomin's own scores are more 'correct' than others. Such a trust in polygenic risk scores may stem from a confusion of population data with personal data.

My main criticism of this book is therefore that Plomin puts too much emphasis on genetic determinism, an idea that has been widely criticized (Esposito, 2017). When it comes to the 50% of variance in complex traits that twin models have shown is associated with variation in environment, he seems to dismiss its importance. He writes that shared environment can be explained in part by genetics, which is plausible. He also states that non-shared environment is 'unsystematic, idiosyncratic, serendipitous events without lasting effects'. Certainly, stochastic factors contribute to an individual's development (Vogt, 2015), but we also know that within identical twin-pair differences in birth weight, a proxy for intrauterine nutrition, show persistent within-pair associations with within-pair differences in susceptibility to conditions such as attention deficit hyperactivity disorder that last across time (Lim et al., 2018). We also know that within-pair differences in self-control persist across time (Cecil et al., 2012).

It is important to note that there is overwhelming evidence that the rates of chronic, noncommunicable diseases have risen steadily during the past two-thirds of a century, driven to a large extent by modifiable environments such as maternal nutrition and obesity and toxins (Fleming et al., 2018). For example, mechanistic studies is the growing field of the Developmental Origins of Health and Disease (DOHaD) have shown that these relationships are mediated in part by non-genetic mechanisms in humans (Lin et al., 2017) and such studies are supported by environmental manipulation of congenic strains of animals (Armitage et al., 2004). We also know that the genetic component of most such diseases is generally less than 50% (Rappaport, 2016).

Plomin states that measuring reported environments is often biased by our perception, which is plausible, although many replicated biological measures of environment do exist. To his credit, he does discuss some of the negative consequences of taking polygenic risk scores too literally; for example, by saying that many would frown on screening out unwanted embryos because of their inferior polygenic risk scores (p. 179).

While Plomin dismisses or ignores evidence for the effect of the environment on complex traits, he does acknowledge that 'environment is important' (p. 32); 'environment is responsible for age-to-age changes [in heritability]'; 'the environment makes a difference' (p. 82); 'attempts to increase equality of [educational] opportunity should focus on reducing shared environmental influence' (p. 96); that policy can shape environment (p. 104); and that environment contributes to lowering blood pressure and obesity. Therefore, while he places an emphasis on genetic determinism, there is a concomitant underappreciation of the environment, especially when encountered in early life, focusing on risks for complex diseases.

Finally, while touching in places on the potential consequences of genetic testing, Plomin stops short of acknowledging the breadth of social, ethical, legal and economic issues associated with genetic testing and the consequences of interpreting polygenic risk scores as he proposes in this book. Such implications for personal genetic screening can be positive—for example, the early identification of disease risk, the discovery of disease pathways that could serve as targets for intervention, and the idea that there are components of traits, like obesity, that individuals do not have control over. However, they can also be negative, in the form of stigmatization and discrimination (Manrique de Lara et al., 2018). By reducing the discussion as Plomin has within his book, there is an absence of wider considerations beyond genetic and environmental factors that could impact upon how individuals, groups and societies develop and live their lives.

In summary, despite an up-to-the minute exploration of the road to personalized genetic risk prediction, Plomin misses the chance to acknowledge that both genes and environment are important and that knowledge of their interaction can boost our chances at understanding and predicting the inset of chronic diseases, and provides the opportunity for meaningful genetic information to be translated and communicated in a way that allows people to make sense of their own genetics. Evidence exists that the public can better understand and respond to a message that genes and environment in combination influence health (Smerecnik, 2010).

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