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New Historical and Philosophical Perspectives on Quantitative Genetics

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Abstract

The aim of this collection is to bring together philosophical and historical perspectives to address long-standing issues in the interpretation, utility, and impacts of quantitative genetics methods and findings. Methodological approaches and the underlying scientific understanding of genetics and heredity have transformed since the field's inception. These advances have brought with them new philosophical issues regarding the interpretation and understanding of quantitative genetic results. The contributions in this issue demonstrate that there is still work to be done integrating old and new methodological and conceptual frameworks. In some cases, new results are interpreted using assumptions based on old concepts and methodologies that need to be explicitly recognised and updated. In other cases, new philosophical tools can be employed to synthesise historical quantitative genetics work with modern methodologies and findings. This introductory article surveys three general themes that have dominated philosophical discussion of quantitative genetics throughout history: 1. How methodologies have changed and transformed our knowledge and interpretations; 2. Whether or not quantitative genetics can offer explanations relating to causation and prediction; 3. The importance of defining the phenotypes under study. We situate the contributions in this special issue within a historical framework addressing these three themes.

New Historical and Philosophical Perspectives on Quantitative Genetics

The vast majority of human traits are thought to be quantitative, polygenic, and complex. They vary continuously within populations, and their variation is due to a complex interplay of genetic and environmental contributions. This seems to be true for physical traits like weight and human stature as well as for psychological and personality differences, behavioural tendencies, and many health and disease outcomes. Traditionally, quantitative traits have stood in opposition to qualitative traits (though see Serpico 2020 for a challenge to this dichotomy). Qualitative traits are categorical, such as the absence or presence of a disease, or white or red eye colour in drosophila. They are often caused by variation at just one part of the genome, and are the exception rather than the norm for human and animal variation (OMIA; OMIM).

Understanding quantitative traits, including how and to what extent genes influence their varied presentations, has been the primary concern of quantitative genetics since the field's infancy. Although quantitative genetics has been both influential and controversial, its conceptual and disciplinary history has received surprisingly little systematic attention from historians and philosophers of science, with the result that major questions about its history - and its legacies - have remained unaddressed. Recent works in the history and philosophy of science are leading the scientific community to a questioning of received views on a range of topics related to the conceptual, methodological, and disciplinary sources of quantitative genetics. Especially pressing is the need for a more comprehensive perspective on the longstanding and apparently unbridgeable divide between quantitative genetics and developmental biology: while the first is widely understood as a science about statistical properties of biological populations, the second takes into account how individual organisms are produced by the interaction between their genotype and the environment over time. This connects to the question of whether theoretical assumptions and methods from early quantitative genetics are tenable in the context of contemporary biology, epigenetics, and systems biology.

The contributions in this collection cover a variety of issues, including: historically open questions on the transition from early to modern genetics, together with controversies on the unification of Mendelian genetics and biometrics; methodological and empirical limitations involved in the transition from older, family-based, and newer molecular methods; questions regarding the epistemological justification and utility of different genetic methodologies; theoretical debates about the causal interpretation of the results of quantitative genetics; conceptual issues on how to understand and define the complex phenotypes investigated by quantitative geneticists, especially behavioural traits like mental disorders and human intelligence; and reflections on the societal, ethical, and economic implications of quantitative genetics data.

1. The Historical Development of Quantitative Genetics

Quantitative genetics was born in the early decades of the twentieth century thanks to the efforts of a number of scholars, among which, William Bateson, Hugo de Vries, Edward East, Wilhelm Johannsen, Herman Nilsson-Ehle, Karl Pearson, Reginal Punnett, Tine Tammes, Raphael Weldon, and George Yule. All these authors engaged in a scientific debate about the hereditary origins of similarities and differences among organisms, based on the work and ideas of Charles Darwin (1809-1882), Francis Galton (1822-1911), and Gregor Mendel (1822-1884).

Galton, in particular, is widely considered the father of biometrics, a branch of empirical sciences concerned with the measurement and investigation of human characteristics. Traits like height and weight - but also psychological and behavioural traits like intelligence - can be

operationalised through quantitative metrics and values. For these traits, all gradations within a certain range can be observed - for instance, individual variation in stature can be represented on a single, continuous dimension. Most of Galton's work is dedicated to the origins of phenotypic similarities and differences among human beings. He understood that the development of quantitative traits does not depend on the causal effect of single genes, but is rather due to many factors. He thus proposed that individual differences in complex traits are influenced by two independent sources of variation: *nature* and *nurture*.

For several decades, scholars working at the crossroad of genetics and biometrics debated how to reconcile the study of complex traits with the observation that some traits - like those analysed in Mendel's studies - appear to be influenced by single genes (see Griffiths & Stotz 2013; Jamienson & Radick 2013; Norton 1975; Porter 2014; Provine 1971; Roll-Hansen 1978; Schwartz 2009). Although several scholars contributed to this reconciliation, the unification of Mendelism and biometrics is usually attributed to Fisher's *infinitesimal model* (1918), according to which variation in quantitative traits is due to the small and additive effect of many independent alleles. Fisher's model soon became the cornerstone of quantitative genetics and contributed to the mathematical foundation of the Modern Synthesis.

Charles Pence's paper (2022) in this collection engages with debates that took place among Mendelians and biometricians at the dawn of quantitative genetics, a period of rapid scientific progress where scholars were negotiating the basic architecture of future genetics. The central concept on which Pence focuses is that of *reversion*, also known as "atavism" and "regression". Reversion denoted cases where organisms presented traits that had not been expressed in their lineage for many generations. This was an extensively observed empirical phenomenon that attracted the attention of scholars like Darwin and Galton; but, interestingly, reversion eventually ceased to be perceived as an intriguing issue, to the point that Fisher did only consider it in its historical context. Pence's analysis reveals that this particular instance of scientific progress was facilitated by conceptual and methodological changes that channelled the early biologically-oriented evolutionary theory into its statistical and mathematical legacies: population and quantitative genetics.

A second topic discussed in this collection is the historical development of the methods of quantitative genetics and the philosophical controversies surrounding them. In contrast with so-called simple traits, like those analysed by Mendel in agricultural contexts, the development of quantitative traits cannot be experimentally manipulated in our species as we do with plants or rodents. Galton and the biometricians thus devised statistical methods, such as the analysis of correlations among relatives, aimed at capturing the phenotypic effects of heredity in such traits. This early work provided the basis for what came to be known as *heritability studies,* a set of methodologies that has been used for decades to assess the relative importance of nature and nurture. Heritability comes in values that range from 0 and 1 (or from 0 to 100%) to indicate the portion of phenotypic variance that is accounted for by genetic variance.

Although various notions of heritability exist (Jacquard 1983), most literature refers to two concepts originally introduced by Jay Lush (1945, 1949): *broad-sense heritability* (H2) and *narrow-sense heritability* (h2). The former refers to genetic variation in the entire genotype, which includes the effects of non-additive relationships between alleles (e.g., dominance and epistasis), and is thus more relevant in the study of asexual reproduction. The latter, instead, only concerns *additive* genetic effects and was introduced as a breeding value coefficient to predict how much a population will change over generations. For instance, if h2 is 100% for a trait - meaning that the phenotypic variance is entirely accounted for by genetic variance - then the value of the trait in the offspring will be midway between the parental values (Schaffner 2016; for a historical reconstruction, see Turkheimer & Downes 2021).

Many human heritability estimates are derived from the study of siblings and identical twins, including some sibling pairs who have been reared apart and/or adopted into new homes.

These studies provide a sort of 'natural experiment' to observe the effects of heredity and environment on related individuals. Here, a typical method consists of comparing the correlations between the phenotypes of individuals with different degrees of relatedness. For instance, we can compare the correlations (*r*) in IQ between pairs of identical (monozygotic, MZ) and non-identical (dizygotic, DZ) twins according to the formula [h2 = 2(*r*MZ - *r*DZ)]. For instance, if the IQ correlation for MZ twins is 50%, and DZ twins is 30%, the heritability of IQ will be 40%.

Over the twentieth century, hundreds of heritability studies were conducted on human populations, ranging from studies of physical traits to somatic diseases and mental disorders. Eventually the dominant view emerged that, in general, both nature and nurture matter, with heritability values ranging between 40% and 80% for most complex traits (Bouchard 2004; Knopik et al. 2017; Polderman et al. 2015). More specifically, heritability studies suggest that every human trait - behaviours included - is heritable to some degree, meaning that part of the variation in such traits is statistically associated with genetic variation. This is described by what Eric Turkheimer (2000) called "the first law of behavioural genetics."

Although the epistemological meaning and socio-ethical implications of these data have been discussed intensely, a full consensus is yet to be achieved. Much controversy has shrouded the methodological basis of heritability studies, but even more debated is their philosophical and biological interpretation (Block 1995; Downes & Matthews 2019; Eysenck & Kamin 1981; Kaplan 2015; Kempthorne 1978; Lewontin 1974; Oftedal 2005; Tabery 2014).

Pierrick Bourrat's paper (2022) analyses two notions of heritability, one deriving from quantitative genetics (the "variance approach") and the other from the biometric tradition (the "regression approach"). The author argues that these two notions have partly different explanatory aims, provide conflicting answers to similar questions, and have different connections with causality. He then explores the possibility of unifying the two under a single notion and puts this notion at work in the study of the heritability of gut microbiome.

Debates over the methodology of quantitative genetics have been exacerbated by the advancement of genetics technologies, particularly after the conclusion of the Human Genome Project. Such a huge scientific enterprise provided the basis for investigating the molecular basis of heritability. In the last couple of decades, genome-wide association studies (GWAS) have thus dominated the field thanks to the possibility of efficiently analysing the association between phenotypic variation and variation at the genomic level in large populations of individuals. GWASs investigate the correlation between phenotypic variation and genetic variation at the nucleotide sequence level, associating single nucleotide polymorphisms (SNPs) with trait differences. Despite pervasive enthusiasm in the field, the attempt to reframe heritability findings in genomic causal terms has revealed to be more problematic than expected.

One widely discussed problem for GWASs is known as *missing heritability* (Eichler et al. 2010; Maher 2008; Manolio et al. 2009). In short, there is a gap between the heritability estimated through classical family-based studies and the heritability accounted for by the SNPs that have been found to be associated with the traits' variation. Researchers have suggested several potential explanations for such a gap, such as the necessity of methodological improvements (e.g., larger sample sizes to increase statistical power) but also theoretical issues.

In this collection, **Lucas Matthews and Eric Turkheimer** (2022) make the case that there are three separate "legs" of the missing heritability problem that researchers need to address: the numerical gap, the mechanism gap, and the prediction gap. Matthews and Turkheimer argue that, despite the often optimistic opinion of many quantitative geneticists, the missing heritability problem is not going to disappear anytime soon because it originates from profound theoretical and methodological differences between traditional and molecular methods.

2. Causation and Prediction

A major question that has engaged philosophers and theoretical biologists in the field concerns whether the notion of heritability - and quantitative genetic data more generally - can be understood *causally* (Griffiths & Stotz 2013; Lynch 2021). Thus, it is no surprise that causation and prediction emerged as a central theme in this special issue. Philosophers and scientists continue to discuss whether quantitative genetic methods can demonstrate causation from statistical, population-based analyses. And, if so, what kind of causal relationship is represented or discovered? What kind of predictive utility do these results allow for? These questions initially sparked controversy for traditional family-based methods and are now being discussed in light of more recent molecular methods.

Qiaoying Lu and Pierrick Bourrat (2022) tackle this central question: what is the exact meaning of heritability estimates, and can they count as causal? They show that heritability models can be reframed using a structural causal modelling (SCM) framework and argue that, in additive cases where gene-environment interplay is absent, heritability can be interpreted as reflecting genetic causation. They also argue that SCMs provide a link between population-level variance related causal claims and individual-level mechanism related causal claims. This link could provide a promising tool in the future of quantitative genetics, as an integration of traditional heritability and molecular approaches leads to the integration of variance partitioning and mechanism-elucidating methods.

Lucas Matthews's paper (2022) focuses on the generality of causal claims that can be provided by heritability analyses. In 1974, Richard Lewontin published a seminal paper discussing the interpretation and utility of heritability estimates derived from family-based designs. He concluded that heritability estimates were not useful, in part because of the problem of *locality*. Locality reflects the uniqueness of heritability estimates, as they are indexed to the particular population studied. Lewontin argued that an estimate from one population could not be used to make inferences about other populations because of this feature, and thus provided very limited causal information. Matthews examines the problem of locality in reference to more modern quantitative genetics techniques such as GWAS, SNPs heritability, and polygenic risk scores. Discussion of these newer methods has centred on the problem of *portability* - can the results of one study be 'ported' to other contexts? Matthews proposes some similarities between locality and portability: they share similar conceptual underpinnings relating to generalisability, and have remarkably similar social and political implications such as the way genetic results can be used for racist agendas. However, there are distinct methodological and conceptual components to the two concepts, including portability's focus on predictive accuracy, which is missing in discussions of locality.

Jonathan Kaplan and Eric Turkheimer (2021) discuss causation in regard to GWASs. First, they outline multiple ways that SNPs may be associated with phenotypes at a population level, including spurious associations, and via gene-environment covariance. The latter are cases where genes predispose individuals to develop in certain environments, indirectly causing phenotypic differences. Contrary to recent philosophical discussion (Lynch 2017, Lynch & Bourrat 2017), the authors argue that in some of these paradigmatic cases the environment should be the causal focus rather than genes, as this better coheres with intuitions about causation and explanation.

They then turn to causation at an individual level. What can GWAS results say about how genes act at an individual level? To address this question, Kaplan and Turkheimer draw an analogy with the 'quincunx' or 'Galton Board.' In a quincunx, individual pins casually influence the location of balls as they move through the machine. The distribution of a population of balls in a machine can be predicted by understanding 'biases' in the constituent pins (attributes of the pins that will make the ball more likely to bounce in a given direction).

However, this causal influence is probabilistic, and the position of any given ball cannot be determined by the position and biases of a set of pins. For an individual ball, its outcome may be probabilistically calculated, though the actual trajectory of the ball through the machine could not. This is akin to SNP-values probabilistically influencing phenotypic outcomes. GWAS can illustrate population level distributions of a trait, and their association with certain SNPs. Polygenic scores for individuals may be calculated using weighted SNP values, but mechanistic information about the causal processes underlying gene action is not available.

The authors argue that this kind of information is not explanatorily useful in an individual context because of the probabilistic nature and complexity of genetics in development.

Gry Oftedal's paper (2022) also discusses the causal effects of SNPs, though through a different lens. In discussions of causation in this field most authors take a position either defending or rejecting the idea that genetic information derived from quantitative genetics is causal in nature. Oftedal takes a different approach, examining the influence of genes through the lens of *causal selection*. Causal selection is the identification of one or a few causes as more salient or important than others (Hesslow 1988). Instead of focussing on whether a relationship is causal or not, investigations are reframed to identify characteristics of causal relationships which may lend themselves to greater explanatory strength or importance. Oftedal centres her discussion on proportionality - which regards how well a cause is described at the appropriate level in respect to its effect (Woodward 2010). She identifies four different kinds of proportionality which are often used interchangeably in the literature: that causes are commensurate to their effects; that causes are appropriately broad or narrow; that effects are appropriately defined, and that the correct cause is selected from a network. She also suggests three different level hierarchies that can be employed for selecting a proportional causal level. She then applies each of these features to the causal relationship between single nucleotide variations and phenotypic effects.

3. Demarcating and Defining Phenotypes

To make progress in understanding the aetiology of a trait, one must first provide a conceptual account of the phenotype under study. In the case of physical traits like stature, measurement is quite straightforward as individuals' height can be expressed uncontroversially in centimetres or inches. However, when it comes to psychological and psychiatric traits, genetics researchers must rely on indirect measures that depend on complex operationalisation procedures provided by psychometrics.

For instance, genetics studies on major depression and intelligence take into account standardised measures such as the Hamilton scale or various IQ tests, respectively. Although such measures provide practical tools to assess individual differences in psychology, framing a trait's variation as 'quantitative' is by no means neutral from an ontological perspective (e.g., Michell 1997, 2012; Hibberd 2014; Serpico 2018; Ward 2022). Moreover, the conceptualisation of many psychological traits varies widely across research areas, so that their definition is typically surrounded by major disagreements.

Another source of uncertainty in demarcating phenotypic variability is that mental disorders such as major depression and Autism Spectrum Disorder (ASD) are often diagnosed categorically - diagnosis may either occur or not - despite their symptoms appearing to vary on a *continuum* across health and pathology (APA 2013; Jang 2005). Moreover, traits that have been classically considered categorical in nature (such as schizophrenia) are recently being reframed through classical quantitative models like Fisher's (1918) and Falconer's (1965) (see Plomin et al. 2009; Knopik et al. 2017; for some criticisms on such models, see Nelson et al. 2013; Turhkeimer 2011; Serpico 2020).

Finally, coarse-grained phenotypic traits are often related to other traits at different levels of organisation (e.g., neuroendocrine, immunological, molecular), often called *endophenotypes*, each of which can involve different causal mechanisms and etiology. The operationalisation of such traits through a single (or a few) quantitative dimensions might be unable to account for the phenotypic complexity at stake. This might be the case not only both for psychological traits, but also for physical traits like body-mass index (BMI) that are often taken as straightforward quantitative traits (Serpico & Borghini 2021; on phenotypic complexity more generally, see Lemoine 2016).

All of these aspects impact genetics research in the choice of what theoretical models and methodologies are believed to better capture the relationship between genetic and phenotypic variation, as well as how to interpret the data.

Polaris Koi (2021) tackles this problem in relation to Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). The paper scrutinises various conceptual accounts of phenotypic variation in such traits, which behavioural geneticists often describe as falling on a continuum. By unpacking a variety of notions used in this context (e.g., homogeneity, heterogeneity, discreteness, dimension, and spectrum), Koi seeks conceptual clarity and outlines a taxonomy of existing quantitative models of genetic variation, assessing their strengths and limitations.

An understanding of phenotypes has important consequences for what are taken to be the *relevant* causes of phenotypic variation. This is demonstrated in **Oftedal**'s paper in this collection, which, as mentioned above, discusses the circumstances in which single nucleotides identified by GWASs can be understood as causes. One of Oftedal's considerations of proportionality is consideration of the effect - which in quantitative genetics is the phenotype. The author's conclusion is that, in general, SNPs have low explanatory power for variation in complex traits, though they could still be proportional causes of complex traits in an interventionist framework. Oftedal's analysis echoes the worry of other authors (e.g., Turkheimer, 2011; see also Kaplan and Turkheimer 2021, in this collection) that an explanation of complex diseases based on the small effects of thousands of alleles will never be satisfactory for the discovery of genetic aetiology.

Conclusions

The papers in this special issue offer important and relevant contributions to our current understanding of what makes people differ: our nature (genetics) and our nurture (the environment). As the field continues to progress with methodological advances and increasing knowledge of genetic mechanisms - as well as their interaction with non-genetic sources of variation - these contributions provide a timely framework for assessing the explanations offered by quantitative genetic studies, and their implications for the study of human difference.

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