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Key issues in contemporary behavioral genetics

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In this article I give a brief overview of the field of behavior genetics in past and present. I identify several areas of rapid advance, as well as some that are posing problems. The most serious issue currently in need to be addressed is the definition of phenotypes. All too often, certain behavioral constructs are assumed to be evaluated in behavioral tests, without either the test or the construct having been adequately validated. It is most likely that many of the conflicting results and failures to replicate reported in the literature can be traced back to this problem. Validation of behavioral constructs and the ways to test them is urgently needed in both animal and human behavioral and psychiatric genetics.

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Introduction

Behavior genetics is the study of the inheritance of behavioral phenotypes. Many different species have been studied, especially rodents (mice and rats), fruit flies (*Drosophila melanogaster*), worms (*Caenorhabditis elegans*), and humans, with zebrafish (*Danio rerio*) currently catching up swiftly. Especially in the last few decades, progress has been rapid and many new genetic techniques are helping elucidate the role of genetics in the causation of behavior. Many of these advances will be addressed in the other reviews in this issue. In this review I will focus on a few key issues facing contemporary behavior genetics.

Behavior genetics is, in principle, not very different from other subfields of genetics: It is strongly multidisciplinary and interdisciplinary, with contributions from ethology, psychology, neuroscience, ecology, psychiatry, etc., and focuses on a specific class of phenotypes: behavior. Therein, however, also lays its greatest distinction with most other genetics disciplines. Behavior is a phenotype that often is very malleable by factors in an organism's environment and almost invariably is influenced by the actions of multiple genes. Exceptions are some, usually rather severe disorders, such as Huntington's chorea and Fragile X Syndrome, which are caused by mutations in a single crucial gene or genomic region. Needless to say that, apart from these exceptions, the genetic analysis of behavior is made much harder by its complex nature. After all, behavior is the output of the brain, by many magnitudes the most complex structure known.

Looking back: A brief history of behavior genetics

Behavior genetics has a long history. This may sound surprising to many younger colleagues who cannot remember the time that we did not have genetically modified animals or genome-wide association studies (GWAS) and who may think that this is a relatively young field. As a matter of fact, the first research into the inheritance of behavior already took place in the 19th century, with Charles Darwin writing about selective breeding for animal behavior [1] and his cousin Francis Galton working on 'genius' [2]. When Mendel's laws were rediscovered, behavioral phenotypes were among the first to be studied in the light of this revolutionary theory (see, e.g. [3,4]). A seminal event in the history of the field was the publication in 1951 of a book chapter entitled '*The Genetics of Behavior*' [5••], written by Calvin Hall (the 'father' of the widely employed open field test, which he validated as a measure of 'emotionality' [6•]). On the basis of the few studies available at the time, Hall displays an acute insight into the issues and questions facing behavior geneticists that are still valid nowadays. He proposed four main objectives for the field that he termed 'psychogenetics': to determine whether a given behavior is inherited, to determine the number and nature of the genetic factors involved, to locate the gene(s) on the chromosomes, and to find out how the genes act to produce a trait ([5••], p. 304). Although the goals of behavior genetics have been phrased in different ways [7], these are nowadays still the basic questions addressed by animal and human behavior geneticists alike [8].

One important change since the early days of behavior genetics is the increased attention paid nowadays to characteristics of the brain. This neurogenetic approach started with van Abeelen's pharmacogenetic experiments, entailing injections of different psychopharmaca directly into defined brain areas of different selected and inbred strains [9,10•], whereas the study of structural features was pioneered by John Fuller, who selected mice for high and low brain weight and then subsequently

looked for behavioral differences between the resulting lines [11,12], and Richard and Cynthia Wimer, who carried out genetic analyses of hippocampal neuroarchitecture [13–15].

One might perhaps wonder why an article on current issues in behavior genetics starts with an historical overview. The reason for this is that knowledge of our predecessors and their early research often is helpful in understanding current approaches and results. In addition, it is sometimes humbling to see the understanding that already was obtained half a century ago and how relatively little, in many respects, we have advanced since. We still have identified with certainty only a few genes influencing behavioral phenotypes be they normal or pathologic. And, finally, some of the most pressing current problems, such as the validation of behavioral constructs mentioned above, were already with us a long time ago and have hardly been addressed in the intervening time.

Human behavior genetics

While in the early days most behavior geneticists often studied many different species and switched rather freely between animal species and humans, the field has become more fragmented over time. Not only has it become rare for researchers to switch between species, but the field of human behavior genetics has effectively separated into two: one investigates the inheritance of normal behavior and the other studies the genetics of pathologies (a subfield nowadays generally called psychiatric genetics). While psychiatric geneticists mostly concentrate on efforts to localize and identify genes, those studying normal behavior have generally stuck with the traditional quantitative-genetic techniques that attempt to partition the variance present in a population into different sources, both genetic and non-genetic ones. This served the field well in the time that it was controversial to claim that genes could somehow influence (human) behavior. As this is now a generally accepted fact this approach has lost much of its appeal. In addition, these methods have two major flaws, one methodological, the other more conceptual.

The quantitative-genetic approach to estimating variance components for human behavior has been criticized from different sides almost since its inception. The well-known statistician Oscar Kempthorne bemoaned the fact that human genetics, due to obvious ethical constraints, was limited to the analysis of observational data, because experiments are impossible [16]. This same argument was already given by McClearn as far back as 1962 [17], who also noted the weakness of the assumption of random mating. Wahlsten argued that because analysis of variance is insensitive to detecting interactions, one of the fundamental assumptions underlying these analyses, the absence of genotype–environment interactions ($G*E$), cannot even be tested adequately [18]. Indeed, we now know that $G*E$ is often key to how genes influence behavior (e.g., [19,20]; a special case of $G*E$ is when patients react differently to pharmacological treatment depending on their genotypes, e.g., [21,22]). In addition, gene–environment co-variation (that is, the phenomenon where organisms carrying certain genotypes prefer certain environments, the absence of which is another assumption underlying quantitative-genetic analyses) has actually been shown to be very important in humans [23•,24]. As a result, partitioning of phenotypic variance using quantitative-genetic methods, already difficult enough when working with animals, where the experimenter can control the subjects' environment, mate choice, etc., usually carries substantial caveats in non-controlled human populations. Some methods have been developed to include gene–environment interaction and covariation in quantitative-genetic models [25–27], but they are used in only few studies, presumably because of the need for parameters that are not always included in existing large datasets.

However, even if we would accept the validity of variance-partitioning quantitative-genetic analyses of human behavior, there is another, more fundamental problem. This relates to the fact that such variance components are population-specific and environment-specific. That is, estimates of heritability will differ between populations. In addition, any estimate is null and void if, say, a significant change in the environment occurs. For example, until 1953, phenylketonuria (PKU, a single gene metabolic disorder [28]) would inevitably lead to mental retardation. The heritability of PKU-induced mental retardation therefore was equal to 1, that is, all variance in the population was genetically based. Nowadays, however, efficient treatments are available and although the heritability of PKU *on the molecular level* is still very high, the heritability of *PKU-induced mental retardation* is nowadays approaching 0, because most affected patients undergo treatment from an early enough age not to suffer from the debilitating effects of this disorder. In other words, a change in environment (in this case, diet) has caused a dramatic drop in heritability for this phenotype. This example also provides a striking illustration of the fact that heritability does not predict 'treatability'. Some characters with a high heritability are perfectly treatable (like PKU), others pose more of a challenge (e.g., Huntington's chorea [29]). Conversely, the same applies to characters with a very low heritability, which can be easily treatable (like a broken bone) or be more complicated (like viral infections such as AIDS or the common flu).

Therefore, the question can and should be posed what, if anything, it means if a certain behavioral characteristic has a high or low heritability. Even more: does a high or a low heritability have any practical implications that would