Opinion

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A century after Fisher: time for a new paradigm in quantitative genetics

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Quantitative genetics traces its roots back through more than a century of theory, largely formed in the absence of directly observable genotype data, and has remained essentially unchanged for decades. By contrast, molecular genetics arose from direct observations and is currently undergoing rapid changes, making the amount of available data ever greater. Thus, the two disciplines are disparate both in their origins and their current states, yet they address the same fundamental question: how does the genotype affect the phenotype? The rapidly accumulating genomic data necessitate sophisticated analysis, but many of the current tools are adaptations of methods designed during the early days of quantitative genetics. We argue here that the present analysis paradigm in quantitative genetics is at its limits in regards to unraveling complex traits and it is necessary to re-evaluate the direction that genetic research is taking for the field to realize its full potential.

The quantitative genetics paradigm

Nearly a century ago, Sir Ronald Fisher's theoretical advancements established the theory that formed the field of quantitative genetics (Box 1). Since then, the field has been extremely productive while conforming to this central paradigm. However, the anomalous results that are emerging from analyses of large data sets collected using new molecular genetics and genomics technologies cast doubts as to whether the current quantitative genetics paradigm is sufficient to meet the challenges of genetically dissecting complex trait variation. The current models are stretched to their limits and require substantial adjustments to explain and deal with the observations. Here, we argue that the field is now in a crisis and at a point where a new genetics framework is needed that can encompass previous results as well as what are, at present, anomalies (see 'The current crisis'). Genetics is a field of the future, but a paradigm shift is needed to realize its full potential in agriculture, medicine, and evolutionary biology.

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Overall, there is strong resistance to change in this field; considerable efforts are spent on either showing that new data do not present a major anomaly [1,2], even though many of the original assumptions of Fisher no longer hold [3–15] or focusing on data or technologies that do not challenge the paradigm [1,2,16,17]. However, it is difficult to ignore the fact that research utilizing genomic data, in many ways, has outpaced developments in quantitative genetic theory. Therefore, it is timely to look back on what has been achieved, while asking: is the original paradigm the foundation upon which to build the future? Will ideas presented at a time when no molecular data were available be appropriate for not only quantifying the contribution of genes to complex traits, but also guiding solutions to challenges involved in predicting the phenotypes of individuals within a population as well as understanding the genetic architecture of traits expressed in the same individual?

The current crisis: ample challenges for quantitative genetics theory

In 1918, Fisher provided a new conceptual way to think about genetic inheritance that made it possible to interpret the findings in biometrical genetics within the Mendelian schemes of inheritance [18] (Box 1). By establishing the additive paradigm of quantitative genetics, a framework was provided that facilitated the dissection of the genetic

Glossary

Additive approach: the assumption that the contribution of genes to the phenotypic trait are independent of each other and sum up to the total genetic contribution.
Biometrics: the application of statistical analysis to biological data.
Epigenetic effects: genome-linked effects on the phenotype not caused by the DNA sequence.
Epistasis: when the alleles at one locus influence the effects of alleles at other loci [42].
Genetic capacitation: the effect where one allele at a given locus (the capacitator) amplifies the effect of alleles at other loci.
Genome-wide association study (GWAS): analysis that examines the association between the genetic variants at a large number of genotyped loci in the genome with the expression of a trait in the studied population
Genotype–phenotype map (GP map): a schematic representation of the mean phenotypic value for each genotypic class.
Genotypic class: all the individuals in a population that share a common single- or multilocus genotype, depending on context.
Infinitesimal model: a model describing the phenotypic variation in a population as the contribution of an infinite number of genes, each making a small additive contribution to the trait [19].
Variance heterogeneity: when the phenotypic variance differs between genotype classes.

Box 1. Evolution of quantitative and molecular genetics

Pre-genetics: Mendel and biometrics

The field of genetics was founded when the first genotype-to-phenotype mapping was presented in Mendel's pioneering work on peas [81]. In parallel to this, Galton developed ideas on the heritability of phenotypic traits during the mid-1870s [82,83]. After Mendel's work was rediscovered [42], there was an active debate between the biometrician and Mendelian schools of thought, including the use of multilocus GP maps to investigate epistasis [42] (Figure I; Box 2).

The first revolution: Fisher's synthesis

During the early 1900s, the British statistician Ronald Fisher revolutionized the field of genetics by presenting a theory that unified the two schools of thought [18]. His work provided a solid framework for the study of phenotypic variation in populations that has prevailed to this day. Fisher developed the quantitative genetics theory under a simplistic, and mainly statistically motivated, assumption that the genetic variance in a population was due to a large number of Mendelian factors, each making a small additive contribution to a particular phenotype, the so-called 'infinitesimal model' [19]. Although Fisher later also included additional explanatory variables to his models, such as dominance and epistacy, these were primarily statistically motivated nuisance parameters accounting for anomalies, rather than biologically important features. During the past century, quantitative genetics theory has matured [84] and immensely impacted applied fields, such as animal- and plant-breeding programs.

The genomics revolution: from data poor to data rich

The statistical framework developed by Fisher was restricted by the lack of molecular insight. It was not until the 1970s that molecular genetics really developed in earnest and, since then, the technological advances have been rapid. Today, it is technically and economically feasible to trace the hereditary process at single nucleotide resolution, something Fisher could not foresee. To some extent, this development has induced reactions in the quantitative genetics field, such as the development of methods for QTL mapping [20,85–87] and genomic prediction [84,88,89] (Figure I). However, it is necessary to collate molecular genetics and quantitative genetics to re-evaluate whether their historical separation into separate fields within genetics reflects their current relevance to each other.

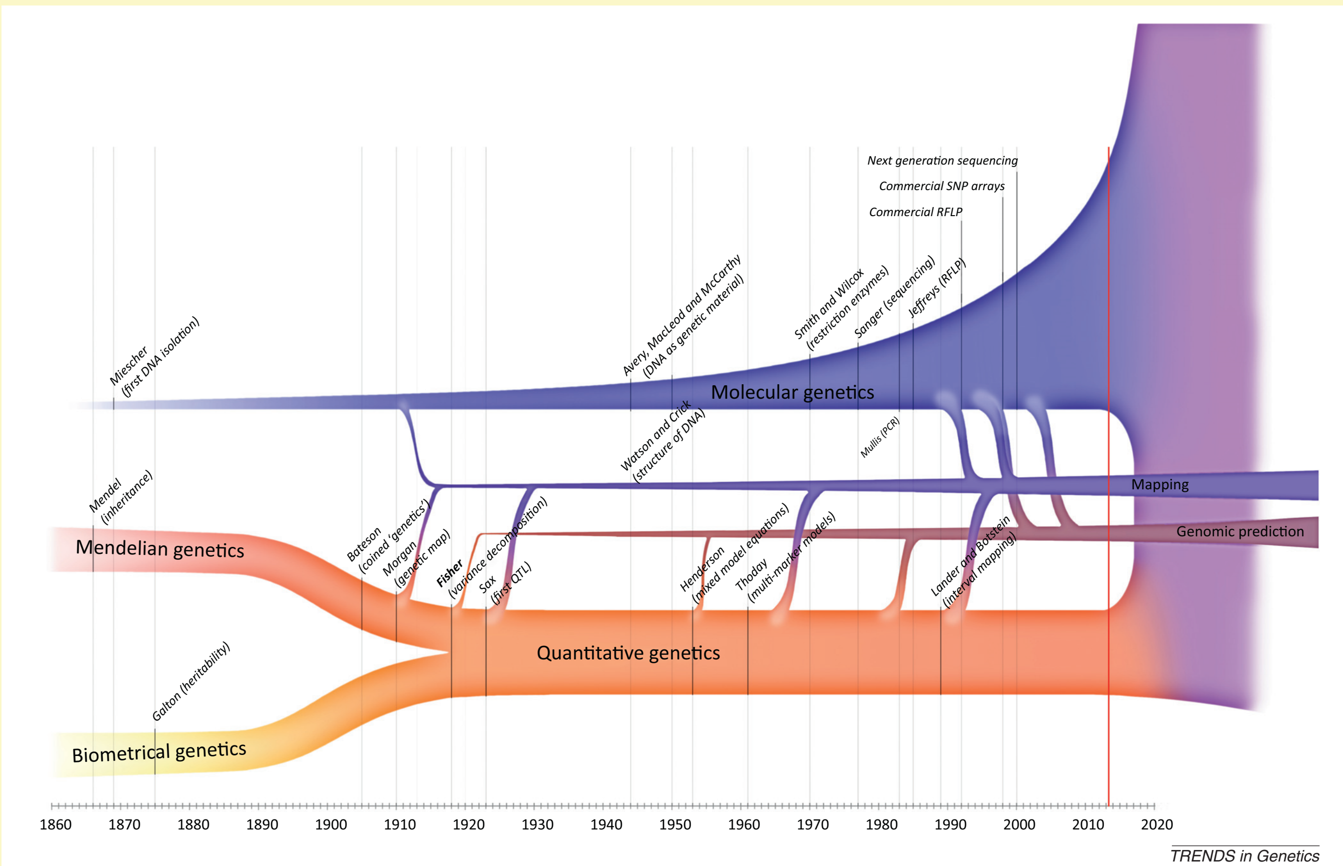

Figure I. Timeline for the fields of molecular and quantitative genetics. The figure illustrates how the new synthesis by Fisher during the early 20th century provided a unified theory for Mendelian and biometrical genetics, how several key discoveries within the fields facilitated the interdisciplinary connections leading to two of the most groundbreaking discoveries in genetics over the past decade, genetic mapping and genomic prediction, and why we believe a new synthesis is needed to provide a common theory that embraces the full width of these two fields. Abbreviations: QTL, quantitative trait locus; RFLP, restriction fragment length polymorphism; SNP, single nucleotide polymorphism.

causes of phenotypic variability within populations into the individually small genetic contributions of large numbers of Mendelian factors [19]. The assumption, that genetic inheritance is mainly additive and that all other genetic and environmental contributions to trait variation are deviations from this, enabled Fisher to formulate a powerful statistical framework that has proven immensely useful. Geneticists have for many years been aware that this model is a simplification that does not accurately reflect the true nature of biological systems. However, because the research and commercial applications that adhered to this theory have remained productive despite this, no major efforts have been made to explore more biologically connected alternatives.

Empirical observations made during the 150 years since Mendel's initial work (Box 1) have, step by step, shown that