

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 capacitor) 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 1; 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 1). 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.

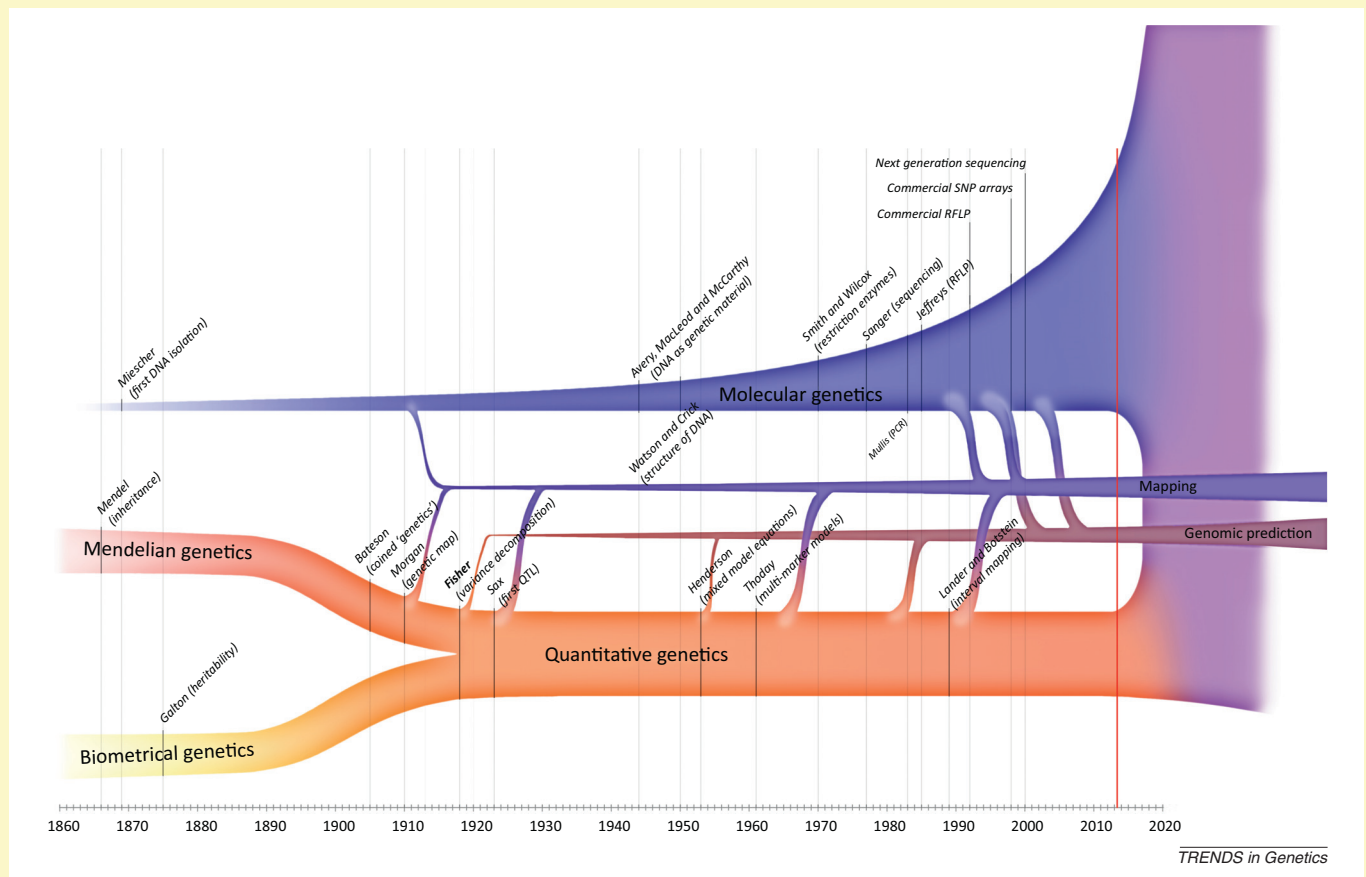


Figure 1. Timeline for the fields of molecular and quantitative genetics. The figure illustrates how the new synthesis by Fisher during the early 20th century provided a unified theory for Mendelian and biometrical genetics, how several key discoveries within the fields facilitated the interdisciplinary 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

many of the basic assumptions made by Fisher when developing his theory are often problematic, and may even result in misleading conclusions. The infinitesimal model was first questioned when it was shown that individual factors make important contributions to trait variation [20], and there are ample examples of intricate genotype–phenotype maps (GP maps), including multiple alleles within a locus, epigenetic effects (see [Glossary](#)), gene–gene interactions (epistasis), and genetic variance control.

There are many suggestions of how to refine the current quantitative genetics framework to address these complicating factors (discussed in more detail below). It has been argued that the route to a more complete understanding of the genetic architecture of complex traits merely requires improvement and fine-tuning, rather than a complete synthesis leading to a new paradigm [16,17,21]. However, that argument does not consider that the underlying infinitesimal model is a pragmatic simplification that severely restricts studies aimed at understanding genetic mechanisms underlying observed phenomena rather than explaining phenotypic variance in populations. Alternatively, we propose that we have the data needed to move beyond population-level genetics and try to construct a new framework, one that is closer to the true biological system.

The missing heritability: an anomaly in genome-wide association studies

The shortcomings of the additive genetic approach become immediately apparent when trying to understand the genetic architecture of complex traits from the outcomes of the large number of genome-wide association studies (GWAS) performed to date [22]. Many of these studies fail to attribute much of the additive genetic variation, as measured by the population-based estimates of the heritability for the studied traits, to the effects of the detected loci [3,23]. Although increased sample sizes and improved scoring of the studied traits are expected to increase the power to detect contributing loci, diminishing returns can be expected from adopting this approach. For example, studies of human height using nearly 200 000 individuals identified 180 contributing loci, but despite having huge sample sizes and an easily measured trait, only approximately 10% of the phenotypic, or 1/8 of the additive genetic, variance could be explained [24]. This study was analyzed by scanning the genome for loci that displayed marginal differences in the phenotypic mean between alternative genotype classes across the study population. The contribution of each locus to the phenotypic variance in the population was then calculated based on the estimated additive allele-substitution effect and the total explained genetic variance was obtained as the sum of the individual effects. Although this analytical approach is computationally efficient, facilitates meta-analyses, and provides population-based statistical estimates of the contributions of the inferred loci on the studied traits, it fails to provide an in-depth exploration of the available data sets. A potential explanation for this is that it does not consider the nonstandard genetic contributions, such as allelic heterogeneity, rare alleles, parent-of-origin effects, genetic interactions, or genetic variance heterogeneity, all of which can make significant contributions to the phenotypic variance.

As a consequence, fewer deviations from the additive model will be detected in the data ([Box 2](#)).

Thus, the genetic effects captured in GWAS are the average, marginal contributions of individual loci or genes to the variance in a population. As such, they do not describe the functional, context-independent, effects of a locus, but rather a statistical, population-dependent, reflection of them [25]. For example, the estimates will change depending on the allele frequency of the studied locus in the population as well as of the loci with which it interacts. Therefore, these estimates will be useful mostly for short-term predictions of changes at the population level (i.e., over time intervals where there are only small changes in the allele frequency), and in the particular population under study, such as in genetic improvement programs in plant and animal populations. However, they will not provide the necessary insight to infer the underlying, functional genetic architecture of the traits required to predict phenotypes of individuals in other populations, as desired in medical diagnostics, or the long-term changes in populations studied in evolutionary biology. To obtain such functional estimates, it is necessary to move beyond the current paradigm and identify and quantify how the effects of a given locus depend on its context. Below, we discuss some types of inheritance pattern, already described in the literature, that challenge the additive model.

Allelic heterogeneity

An emerging feature in many in-depth studies of genotype–phenotype relations is the evolution of several functional alleles at key loci in the genome [26–30]. Contributions of multiple alleles are often overlooked in quantitative genetics because a core assumption in standard GWAS and linkage studies is that of a single causative allele linked to one of the alleles of a bi-allelic marker [31], rather than a series of alleles linked to a multi-allelic marker. Given the rapid development of new techniques for identifying polymorphisms in the genome, it is now possible to both identify and score multiple alleles. The challenge now is to develop an analytical and modeling framework that utilizes, rather than marginalizes, this additional information.

Epigenetic inheritance

Another factor adding to the complexity of the genotype–phenotype relation is epigenetic inheritance, which is now known to affect some phenotypes [32]. Arguably, the best understood mechanism is through imprinting [33,34], which has been investigated in several cases [e.g. insulin growth factor 2 (IGF2) and growth rate in pigs [35,36]; Callipyge locus in sheep [37], and maternal imprinted Dnmt3L in mice [38]]. Recent studies have identified epigenetic factors that lead to heritable variation [39–41]; however, a disparity remains between the methods for finding epigenetic and genetic regulation and, therefore, a new framework for modeling the simultaneous contributions of both to the phenotypes of individuals is required.

Genetic interactions: epistasis

The term ‘epistasis’ was first coined by Bateson in his studies of multilocus GP maps, where he found that the

Box 2. Genotype–phenotype maps revealing genetic architecture

At the core of genetics is the GP map. Ever since Mendel's pioneering work with peas, geneticists have returned to these maps to understand the connection between the genotype and phenotype. Figure 1 is an example of how GP maps can reveal the combined effects of multiple loci on a single phenotype.

The strength, as well as the weakness, of Fisher's quantitative genetics models is that it focuses on reducing the complexity of single and multilocus GP maps into a hierarchical linear model, where additivity is the highest level effect from which all other effects are defined as deviations. This model is efficient in capturing the variance in many GP maps [1], but provides little insight into the genetic architecture. Figure 1A represents a model where the phenotypic distributions for three involved loci are considered independently. Here, the *S* locus displays a mean difference between the genotypes and, consequently, has an additive effect that should be detectable using standard quantitative genetic approaches. However, the full contribution of the locus to the phenotypic variance cannot be described with such methods, because it also has a genetically determined variance heterogeneity. The phenotypic distribution for the alternative alleles at the *R* locus displays a smaller mean

difference than the *S* locus and almost no variance differences. Unless the sample size is large, this locus is unlikely to be detected based solely on its own effects (Figure 1B).

The *Q* locus displays no mean difference between genotypes and, therefore, will not be detectable by current popular methods. However, several novel alternative models are designed to detect these variance-affecting QTL (e.g. [60,90]).

When visualizing the possible two-locus GP maps, nonadditive interactions between the loci can be observed (Figure 1B). Bateson postulated that alleles at one locus could mask the effects of alleles at other loci [42] as observed when multiple loci are investigated simultaneously.

However, the full genetic architecture in this example only becomes clear when the effects of all three loci are investigated simultaneously (Figure 1C); that is, all 27 genotypic classes in this system are visualized. The main effect of the *S* locus is due to capacitating epistasis [71]. Epistasis between the *R* and *Q* loci causes the variance effect seen when the *Q* locus is investigated alone. The example shows that it is necessary to explore various analysis options to explain the full contribution of multiple loci to an observable phenotype.

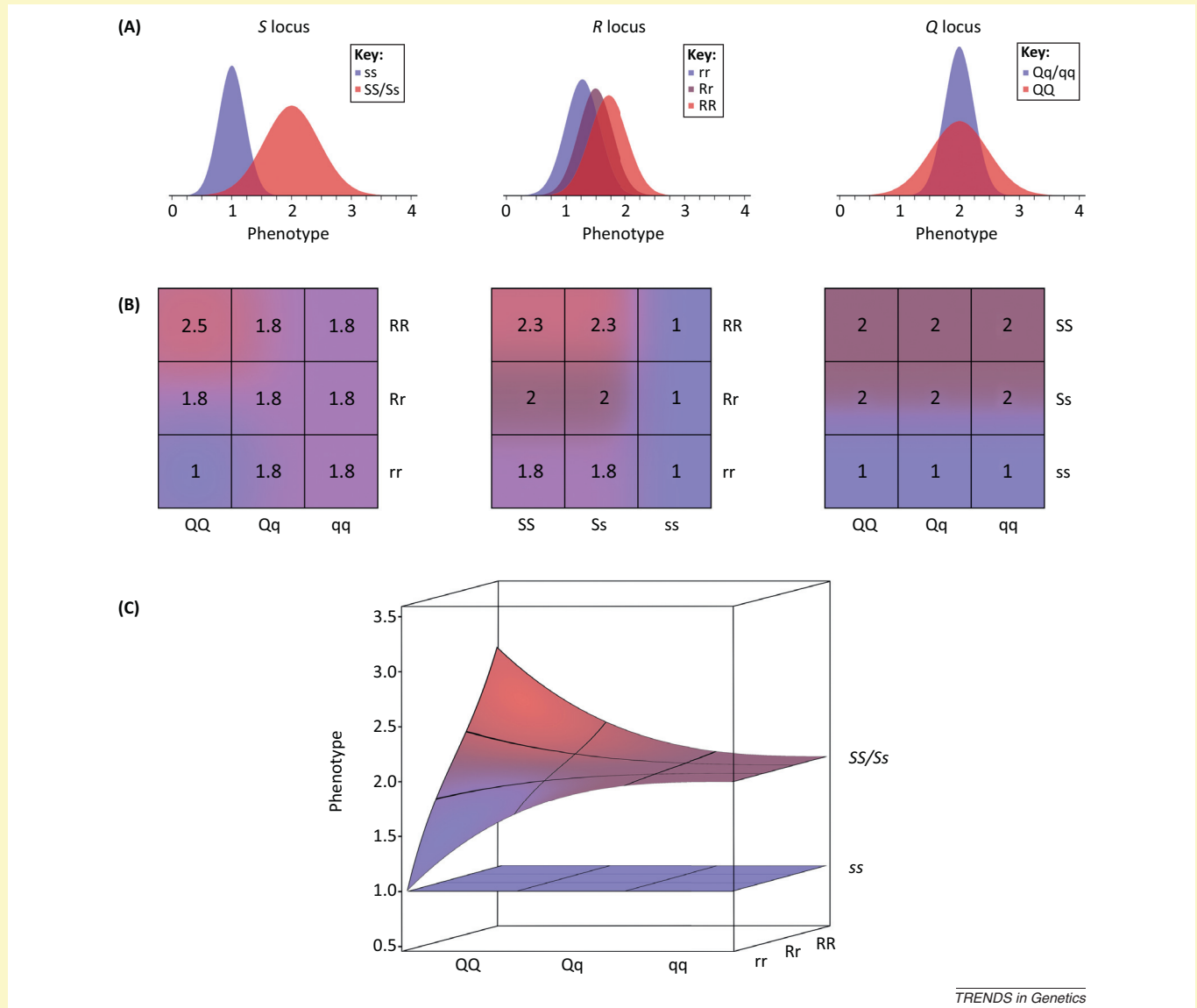


Figure 1. Example of a three-locus system affecting a trait with different genotype–phenotype (GP) representations. **(A)** Phenotype distributions for each locus independently. **(B)** Phenotype distributions for all the possible two-locus interactions. **(C)** Three-locus GP map visualizing all genetic combinations and their effect on the phenotype.

alleles at one locus could mask the effects of alleles at other loci [42]. Following his work, many classical types of genetic interaction have been defined for qualitative traits, including dominant epistasis, duplicate factor epistasis, and complementary epistasis [43–48].

To date, there are many both theoretical and empirical indications that epistasis, as defined by Bateson, may also be an important contributor to the genetic architecture of complex traits. Evidence for epistasis has been found in artificial selection experiments, where the phenotypic variation is often not depleted during long-term selection as rapidly as expected [49]. It has been shown that genetic capacitance might have an important role here to mask or magnify the phenotypic effect of other loci as the allele frequencies change in response to selection (Box 2) [48,50–54]. In addition, classical genetic theory suggests that the continuous nature of phenotypic variation is due to epistasis [15,55]. There is also strong evidence from molecular studies on model organisms [48,55] and network analyses [54,56–58] that indicate that gene–gene interactions are commonplace.

Despite these findings, the general view in current quantitative genetic theory is that epistasis is a nuisance parameter in the genetic model. This means that, regardless of the pattern in the GP map, it only describes the portion of the genetic variance that cannot be explained by the marginal effects of individual loci in the hierarchical genetic effect model. Consequently, many of the GP maps that show an important contribution of interactions to trait expression in individuals often display little epistatic variance [1]. In effect, the current quantitative genetics framework has a built-in bias against inferring epistasis, making it insufficient for identifying and interpreting epistatic effects, as well as for predicting individual phenotypes using data from genetic association or mapping studies.

Genetic variance control

When Fisher developed his genetic models, genetic factors were perceived to act on the mean trait expression in a population. Later, it was shown that genes could also control trait robustness and, more recently, individual loci displaying genetically determined variance heterogeneity between genotypes have been identified [21,59–61]. Such loci, known as variance quantitative trait loci or vQTL for short, contribute to the phenotypic variance in a way that is completely missed in standard GWAS analyses. Variance heterogeneity could emerge from direct effects through disruptions of regulatory systems (evidence for gene expression regulation being under genetic control has been reported [62]) and such individual locus effects have been suggested as a potentially important adaptive mechanism both empirically [63,64] and theoretically [65]. Furthermore, variance heterogeneity could also emerge as a feature of other underlying mechanisms, such as gene-by-environment or epistatic interactions (Box 2). Given that the analyses to detect variance-controlling loci can easily be applied to existing data sets collected for genome-wide association or linkage analyses, we can expect to obtain more empirical insights into the importance of such regulation in the genetic architecture of a wide range of complex traits in the near future.

In defence of the current paradigm

Research within a currently accepted framework usually provides results that are both anticipated and expected, making it, in a practical sense, highly productive. It will naturally be defended on the basis that ‘it works’, while the observed anomalies in data will either be ignored or argued to be unimportant or uncommon exceptions [1,2]. As anomalies become increasingly common, questions are often addressed by focusing on the ‘technical’ aspects of the problem. Thus, the current framework is patched and amended to address the immediate challenges, which for GWAS studies, for example, include rare alleles, copy number variation, and uniquely structured populations and subpopulations [3–15,66].

If such strategies are unsuccessful in resolving the problems, arguments are often raised for collecting more data, which in genetics has meant increasing both the number of samples and the number of markers typed [4,6,7,11,66,67]. However, increasing sample sizes in genetics is, as discussed above, a game of diminishing returns [3] because it is sensitive to allele frequencies in the study population due to the practice of detecting average genotype values [11,14,15]. Subdividing the population and, hence, decreasing the sample sizes, may increase the power to detect loci influencing the phenotype if the subsets have more favorable allele frequencies. One well-known example of bigger data sets not leading to better results is the case of estrogen receptor-negative BRCA1-positive individuals [14].

In summary, the additive approach has, indisputably, proven to be a useful tool for detecting a large number of main effect loci by associating the common phenotypes with the common genotypes in the sample data [1,2,23]. However, despite considerable efforts to collect large sample sizes and modify the statistical models used in the additive genetic framework, the ‘missing’ heritability problem remains. This highlights one of the core pitfalls of continuing along the current path and we argue that developing technical refinements of the current models will not provide a solution. A new approach, albeit more complex, is needed to provide a more general and accurate match between the observed genotypic and phenotypic data without relying on complex adjustments or simplistic assumptions.

Towards a new synthesis in genetics

The main concern when working within an outdated paradigm is the limitations it imposes on our thinking as well as our ability to utilize, rather than discard, findings that are outside its scope. For example, the nature of GWAS focuses almost entirely on finding additive effects, which biases the detection and interpretation of results towards genes that act in a fashion that conforms to this assumption. However, the available molecular evidence indicates that biological systems are anything but additive and that we need to evaluate alternative ways of utilizing the new data to understand the function of the genome. Today, most gene–gene and gene–environment interactions or loci with multiple alleles or epigenetic inheritance are missed or, at best, detected with reduced power. Even when such loci are detected, the explanatory models fail to unravel the true

mechanism underlying the observation. It is clear that the additive approach cannot lead to a deeper understanding of interactions between genes and, as a consequence, predictions on an individual level are limited to those possible using the available, biologically unrealistic models, regardless of the number of markers and individuals used or further refinement of these methods.

The goal of a new paradigm in quantitative genetics should be to disentangle more accurately all the genetic effects, including interactions within the genome and environment that have an effect on one or several phenotypes for each individual, rather than an average for the whole population. For this, novel ideas for analyzing genome data outside of the current paradigm need to be developed *de novo* while considering the insights provided by the recent advances in molecular genetics. This will not only provide a more accurate basis for basic research in genetics and biology, but also lead to better applications in medicine and the industry. It may also revive interest in personalized medicine [68–70].

The key to developing such a new framework for future genetics lies in an improved understanding of how GP maps capture information from the genome that is missed using the current paradigm (Box 2). Analysis of interaction networks requires dissection of GP maps in various dimensions and these need to be constructed, visualized, compared, and understood in relation to their ability to explain the expression of a trait in an individual. This work needs to be unbiased with regard to how many genes are involved and how their effects combine.

Construction of the large number of GP maps needed for this does not require the generation of data sets with more markers in an effort to find rare alleles, but rather carefully planned collections of data sets that contain phenotypes associated with as many genotype combinations from the common and/or known allele variants as possible (Box 2). These data can then be used to explore alternative options for describing how different genotypic classes contribute to the observed phenotype. It is only by designing methods for detecting such functional effects of different combinations of alleles that we can expand understanding of the information provided in high-density genomic data and genome sequences.

Several research groups have realized the need to explore genetic inheritance beyond additivity and, hence, have developed analysis methods to use genomic data for detection of epistasis. A practical first step is ensuring that the analysis is unbiased and that the additive model is not used as the null hypothesis. This needs to be done during the experimental design phase where the population and/or potential data are evaluated for finding epistasis [52,71,72]. These methods include genetic algorithms [73,74] and machine-learning techniques [74–79]. Although these are important first steps towards a completely new synthesis, they all have their limitations, such as not being able to account for available biological information, high computational complexity, or biases often introduced prior to analysis.

Thus, finding complex interaction patterns will require revisiting and extending classical genetics theory and developing new models that can deal with high-dimensional

and big data sets in an efficient way. However, first, it is necessary to change the way geneticists in general perceive how modeling of biological data can and should be done.

Concluding remarks

We advocate that it is time to return to classical genetics and evaluate how to integrate the basic principles of genetic inheritance with the opportunities provided by large-data genomics. The GWA and linkage studies are powerful tools to dissect the genetics of complex traits, but in their current incarnations known facts from molecular genetics are often overlooked when designing the methods used to analyze the collected data. This is, in part, because the generation of molecular data has been more rapid than development of new quantitative genetic theory. Thus, current analysis tools utilized the old quantitative genetics models and statistical frameworks that were available at the time, despite the fact that the theory was developed before the genomics revolution. Over the years, the data sets have grown from single genes or only a few markers into full genomes from hundreds of thousands of individuals. At the same time, insights into the mechanisms underlying multifactorial traits have increased and indicate that we have now reached a stage where we need to explore inheritance beyond additive effects.

Returning to the analysis of GP maps means that they need to be extended beyond Mendelian traits affected by a single gene or pair of genes to also describe correctly more complex relations. With accurate GP maps, genes interacting in metabolic pathways will be easier to identify, which will have several benefits: (i) help the field(s) of metabolomics and/or interactomics; (ii) identify gene groups (and even single regulating genes) as targets for therapy in disease studies; and (iii) expand general understanding of how many genes lead to a phenotype or phenotypes.

Here lies the challenge in future genetics: to derive the models needed to construct a new framework for the field. There is a general belief in society that modern biology, and genetics in particular, will lead to improved quality of life. Lately, concerns have been raised due to the inability of association studies to explain the genetic architectures of complex traits [69,70,80]. To fulfill these big hopes, we suggest implementing three principles when setting up a project for unraveling the genetic architecture of a complex trait: (i) proper design and/or sampling of the experimental population; (ii) insurance of an unbiased analysis scheme; and (iii) use and/or development of the appropriate statistical methods. This will enable us to look beyond the knowledge gained from the current approaches and re-analyze available data sets with new analytical approaches to detect nonadditive genetic effects. This will not only increase basic understanding of the link between DNA and phenotype, but also provide the expected solutions to the grand challenges of future biological science, medicine, and agriculture.

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References

- 1 Hill, W.G. *et al.* (2008) Data and theory point to mainly additive genetic variance for complex traits. *PLoS Genet.* 4, e1000008
- 2 Visscher, P.M. *et al.* (2012) Five Years of GWAS Discovery. *Am. J. Hum. Genet.* 90, 7–24
- 3 Baker, M. (2010) The search for association. *Nature* 467, 1135–1138
- 4 Frazer, K.A. *et al.* (2009) Human genetic variation and its contribution to complex traits. *Nat. Rev. Genet.* 10, 241–251
- 5 Hirschhorn, J.N. and Daly, M.J. (2005) Genome-wide association studies for common diseases and complex traits. *Nat. Rev. Genet.* 6, 95–108
- 6 Eichler, E.E. *et al.* (2010) Missing heritability and strategies for finding the underlying causes of complex disease. *Nat. Rev. Genet.* 11, 446–450
- 7 McCarthy, M.I. *et al.* (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat. Rev. Genet.* 9, 356–369
- 8 Thomas, D. (2010) Gene-environment-wide association studies: emerging approaches. *Nat. Rev. Genet.* 11, 259–272
- 9 Wu, X. *et al.* (2010) A novel statistic for genome-wide interaction analysis. *PLoS Genet.* 6, e1001131
- 10 Crow, J.F. (2010) On epistasis: why it is unimportant in polygenic directional selection. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* 365, 1241–1244
- 11 Rosenberg, N.A. *et al.* (2010) Genome-wide association studies in diverse populations. *Nat. Rev. Genet.* 11, 356–366
- 12 McPherson, J. (2009) Next-generation gap. *Nat. Methods* 6, 2–5
- 13 de Los Campos, G. *et al.* (2010) Predicting genetic predisposition in humans: the promise of whole-genome markers. *Nat. Rev. Genet.* 11, 880–886
- 14 Kraft, P. and Haiman, C.A. (2010) GWAS identifies a common breast cancer risk allele among BRCA1 carriers. *Nat. Genet.* 42, 819–820
- 15 Moore, J.H. and Williams, S.M. (2009) Epistasis and its implications for personal genetics. *Am. J. Hum. Genet.* 85, 309–320
- 16 Yang, J. *et al.* (2011) REPORT GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* 88, 76–82
- 17 Li, Y. *et al.* (2010) Critical reasoning on causal inference in genome-wide linkage and association studies. *Trends Genet.* 26, 493–498
- 18 Fisher, R.A. (1918) The correlation between relatives on the supposition of Mendelian inheritance. *Trans. R. Soc. Edinb.* 52, 399–433
- 19 Fisher, R.A. (1930) *The Genetical Theory of Natural Selection*, Clarendon
- 20 Sax, K. (1923) The association of size differences with seed-coat pattern and pigmentation in *Phaseolus vulgaris*. *Genetics* 8, 552–560
- 21 Yang, J. *et al.* (2012) Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat. Genet.* 44, 369–375 1–10
- 22 Hindorf, L. *et al.* (2013) *A Catalog of Published Genome-Wide Association Studies*, National Human Genome Research Center
- 23 Manolio, T.A. *et al.* (2009) Finding the missing heritability of complex diseases. *Nature* 461, 747–753
- 24 Allen, H.L. *et al.* (2010) Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature* 467, 832–838
- 25 Álvarez-Castro, J.M. and Carlborg, Ö. (2007) A unified model for functional and statistical epistasis and its application in quantitative trait loci analysis. *Genetics* 176, 1151–1167
- 26 Johansson Moller, M. *et al.* (1996) Pigs with the dominant white coat color phenotype carry a duplication of the KIT gene encoding the mast/stem cell growth factor receptor. *Mamm. Genome* 7, 822–830
- 27 Pielberg, G. *et al.* (2002) Unexpectedly high allelic diversity at the KIT locus causing dominant white color in the domestic pig. *Genetics* 160, 305–311
- 28 Hellström, A.R. *et al.* (2010) Sex-linked barring in chickens is controlled by the CDKN2A/B tumour suppressor locus. *Pigment Cell Melanoma Res.* 23, 521–530
- 29 Jeon, J.T. *et al.* (1999) A paternally expressed QTL affecting skeletal and cardiac muscle mass in pigs maps to the IGF2 locus. *Nat. Genet.* 21, 157–158
- 30 McPherron, A.C. and Lee, S.J. (1997) Double muscling in cattle due to mutations in the myostatin gene. *Proc. Natl. Acad. Sci. U.S.A.* 94, 12457–12461
- 31 Flister, M.J. *et al.* (2013) Identifying multiple causative genes at a single GWAS locus. *Genome Res.* <http://dx.doi.org/10.1101/gr.160283.113>
- 32 Daxinger, L. and Whitelaw, E. (2012) Understanding transgenerational epigenetic inheritance via the gametes in mammals. *Nat. Rev. Genet.* 13, 153–162
- 33 Reik, W. and Walter, J. (2001) Genomic imprinting: parental influence on the genome. *Nat. Rev. Genet.* 2, 21–32
- 34 Ferguson-Smith, A.C. (2011) Genomic imprinting: the emergence of an epigenetic paradigm. *Nat. Rev. Genet.* 12, 565–575
- 35 Nezer, C. *et al.* (2003) Haplotype sharing refines the location of an imprinted quantitative trait locus with major effect on muscle mass to a 250-kb chromosome segment containing the porcine IGF2 gene. *Genetics* 165, 277–285
- 36 Nezer, C. *et al.* (1999) An imprinted QTL with major effect on muscle mass and fat deposition maps to the IGF2 locus in pigs. *Nat. Genet.* 21, 155–156
- 37 Georges, M. *et al.* (2013) Cis- and Trans-Effects Underlying Polar Overdominance at the Callipyge Locus. In *Epigenetics and Complex Traits* (Naumova, A.K. and Greenwood, C.M.T., eds), pp. 89–106, New York, Springer
- 38 Bourc'his, D. *et al.* (2001) Dnmt3L and the establishment of maternal genomic imprints. *Science* 294, 2536–2539
- 39 Johannes, F. *et al.* (2009) Assessing the impact of transgenerational epigenetic variation on complex traits. *PLoS Genet.* 5, e1000530
- 40 Heyn, H. *et al.* (2013) DNA methylation contributes to natural human variation. *Genome Res.* 23, 1363–1372
- 41 Ziller, M.J. *et al.* (2013) Charting a dynamic DNA methylation landscape of the human genome. *Nature* 500, 477–481
- 42 Bateson, P. (1909) *Mendel's Principles of Heredity*, Cambridge University Press
- 43 Phillips, P.C. (2008) Epistasis: the essential role of gene interactions in the structure and evolution of genetic systems. *Nat. Rev. Genet.* 9, 855–867
- 44 Haley, C.S. and Carlborg, Ö. (2004) Epistasis: too often neglected in complex trait studies? *Nat. Rev. Genet.* 5, 618–625
- 45 Cordell, H.J. (2002) Epistasis: what it means, what it doesn't mean, and statistical methods to detect it in humans. *Hum. Mol. Genet.* 11, 2463–2468
- 46 Wolf, J.B. *et al.* (2000) *Epistasis and the Evolutionary Process*, Oxford University Press
- 47 Wade, M.J. *et al.* (2001) Alternative definitions of epistasis: dependence and interaction. *Trends Ecol. Evol.* 16, 498–504
- 48 He, X. *et al.* (2010) Prevalent positive epistasis in *Escherichia coli* and *Saccharomyces cerevisiae* metabolic networks. *Nat. Genet.* 42, 272–276
- 49 Eitan, Y. and Soller, M. (2004) Selection induced genetic variation. In *Evolutionary Theory and Processes: Modern Horizons* (Wasser, S.P., ed.), pp. 153–176, Springer
- 50 Boyko, A.R. *et al.* (2010) A simple genetic architecture underlies morphological variation in dogs. *PLoS Biol.* 8, e1000451
- 51 Buckler, E.S. *et al.* (2009) The genetic architecture of maize flowering time. *Science* 325, 714–718
- 52 Carlborg, Ö. *et al.* (2006) Epistasis and the release of genetic variation during long-term selection. *Nat. Genet.* 38, 418–420
- 53 Johansson, A. *et al.* (2010) Genome-wide effects of long-term divergent selection. *PLoS Genet.* 6, e1001188
- 54 Costanzo, M. *et al.* (2010) The genetic landscape of a cell. *Science* 327, 425–431
- 55 Flint, J. and Mackay, T.F.C. (2009) Genetic architecture of quantitative traits in mice, flies, and humans. *Genome Res.* 19, 723–733
- 56 Wang, K. *et al.* (2010) Analysing biological pathways in genome-wide association studies. *Nat. Rev. Genet.* 11, 843–854
- 57 Barabási, A-L. *et al.* (2011) Network medicine: a network-based approach to human disease. *Nat. Rev. Genet.* 12, 56–68
- 58 Swarup, S. *et al.* (2013) Analysis of natural variation reveals neurogenetic networks for *Drosophila* olfactory behavior. *Proc. Natl. Acad. Sci. U.S.A.* 110, 1017–1022
- 59 Weller, J. *et al.* (1988) Linkage analysis of quantitative traits in an interspecific cross of tomato (*Lycopersicon esculentum* x *Lycopersicon pimpinellifolium*) by means of genetic markers. *Genetics* 118, 329–339
- 60 Shen, X. *et al.* (2012) Inheritance beyond plain heritability: variance-controlling genes in *Arabidopsis thaliana*. *PLoS Genet.* 8, e1002839
- 61 Geiler-Samerotte, K. *et al.* (2013) The details in the distributions: why and how to study phenotypic variability. *Curr. Opin. Biotechnol.* 24, 752–759 <http://dx.doi.org/10.1016/j.copbio.2013.03.010>

- 62 Ansel, J. *et al.* (2008) Cell-to-cell stochastic variation in gene expression is a complex genetic trait. *PLoS Genet.* 4, e1000049
- 63 Zhang, Z. *et al.* (2009) Positive selection for elevated gene expression noise in yeast. *Mol. Syst. Biol.* 5, 299
- 64 Wang, Z. and Zhang, J. (2011) Impact of gene expression noise on organismal fitness and the efficacy of natural selection. *Proc. Natl. Acad. Sci. U.S.A.* 108, E67–E76
- 65 Pettersson, M. *et al.* (2012) Selection on variance controlling genes: adaptability or stability. *Evolution* 66, 3945–3949
- 66 Wray, N.R. *et al.* (2013) Pitfalls of predicting complex traits from SNPs. *Nat. Rev. Genet.* 14, 507–515
- 67 Lanktree, M.B. *et al.* (2011) Meta-analysis of dense genecentric association studies reveals common and uncommon variants associated with height. *Am. J. Hum. Genet.* 88, 6–18
- 68 Flint, J. and Mott, R. (2001) Finding the molecular basis of quantitative traits: successes and pitfalls. *Nat. Rev. Genet.* 2, 437–445
- 69 van Hoek, M. *et al.* (2008) Predicting type 2 diabetes based on polymorphisms from genome-wide association studies. *Diabetes* 57, 3122–3128
- 70 Hall, W.D. *et al.* (2010) Being more realistic about the public health impact of genomic medicine. *PLoS Med.* 7, e1000347
- 71 Pettersson, M. *et al.* (2011) Replication and explorations of high-order epistasis using a large advanced intercross line pedigree. *PLoS Genet.* 7, e1002180
- 72 Huang, W. *et al.* (2012) Epistasis dominates the genetic architecture of *Drosophila* quantitative traits. *Proc. Natl. Acad. Sci. U.S.A.* 109, 15553–15559
- 73 Mooney, M. *et al.* (2011) The GA and the GWAS: using genetic algorithms to search for multi-locus associations. *IEEE/ACM Trans. Comput. Biol. Bioinform.* 9, 899–910
- 74 Nelson, R.M. *et al.* (2013) Higher order interactions: detection of epistasis using machine learning and evolutionary computation. In *Genome-Wide Association Studies and Genomic Prediction* (Gondro, C., van der Werf, J. and Hayes, B., eds), pp. 499–518, Springer
- 75 Wang, L. *et al.* (2011) Gene set analysis of genome-wide association studies: methodological issues and perspectives. *Genomics* 98, 1–8
- 76 Ritchie, M. *et al.* (2004) Genetic programming neural networks as a bioinformatics tool for human genetics. In *Genetic and Evolutionary Computation—GECCO 2004* (Deb, K., ed.), pp. 438–448, Springer
- 77 Szymczak, S. *et al.* (2009) Machine learning in genome-wide association studies. *Genet. Epidemiol.* 33 (Suppl. 1), S51–S57
- 78 Han, B. *et al.* (2010) A Markov blanket-based method for detecting causal SNPs in GWAS. *BMC Bioinformatics* 11 (Suppl. 3), S5
- 79 Fridley, B.L. and Biernacka, J.M. (2011) Gene set analysis of SNP data: benefits, challenges, and future directions. *Eur. J. Hum. Genet.* 19, 837–843
- 80 Bogardus, C. (2009) Missing heritability and GWAS utility. *Obesity* 17, 209–210
- 81 Mendel, G. (1866) Experiments in plant hybridization (1865). *Proceedings of the Natural History Society of Brünn* IV, 3–47
- 82 Galton, F. (1876) A theory of heredity. *J. Anthropol. Inst.* 5, 329–348
- 83 Galton, F. (1877) Typical laws of heredity. *Nature* 15, 492–495 512–514, 532–533
- 84 Henderson, C. (1953) Estimation of variance and covariance components. *Biometrics* 9, 226–252
- 85 Morgan, T. (1911) Random segregation versus coupling in Mendelian inheritance. *Science* XXXIV, 1911
- 86 Morgan, T.H. (1911) Chromosomes and associative inheritance. *Science* 34, 384
- 87 Lander, E.S. and Botstein, D. (1989) Mapping Mendelian factors underlying quantitative traits using RFLP linkage maps. *Genetics* 121, 185–199
- 88 Fisher, R.A. (1941) Average excess and average effect of a gene substitution. *Ann. Eugen.* 11, 53–63
- 89 Meuwissen, T. and Goddard, M.E. (1996) The use of marker haplotypes in animal breeding schemes. *Genet. Sel. Evol.* 28, 161–176
- 90 Rönnegård, L. and Valdar, W. (2011) Detecting major genetic loci controlling phenotypic variability in experimental crosses. *Genetics* 188, 435–447