Mechanism schemas and the relationship between biological theories

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Abstract

Current accounts of the relationship between classical genetics and molecular biology favor the 'explanatory extension' thesis, according to which molecular biology elucidates aspects of inheritance unexplained by classical genetics. I identify however an unresolved tension between the 'explanatory extension' account and examples of 'explanatory interference' (cases when the accommodation of data from molecular biology results in a more precise genotyping and more adequate classical explanations). This paper provides a new way of analyzing the relationship between classical genetics and molecular biology capable of resolving this tension. The proposed solution makes use of the properties of mechanism schemas and sketches, which can be completed by elucidating some or all of their remaining 'black boxes' and instantiated via the filling-in of phenomenon-specific details. This result has implications for the reductionism-antireductionism debate since it shows that molecular elucidations have a positive impact on classical explanations without entailing the reduction of classical genetics to molecular biology.

Keywords: explanation, genetics, mechanism, mechanism schema, philosophy of biology, reductionism

1. Introduction

It is widely accepted by scientists (Morange 1998; Muller 1951) and philosophers (Darden 1991; 2006; Schaffner 1969; Waters 2004) alike that the development of molecular biology was driven by an attempt to answer the questions: "What is the physical nature of

genes?" and "How do genes determine phenotypes?" Such questions fall outside the immediate explanatory scope of classical genetics, which is mainly concerned with the transmission of inherited traits (Morgan 1935; Moss 2003; Waters 2004).

Given the seemingly distinct explanatory scopes of classical genetics and molecular biology, Philip Kitcher (Culp and Kitcher 1989; Kitcher 1982, 357; 1999, 199) proposed the 'explanatory extension' thesis, according to which molecular biology explains aspects of inheritance not explained by classical genetics. Kitcher (1989) embedded this thesis in the larger context of his own unificationist account of explanation, which relies on the notion that explanation requires a particular kind of deductive argument schema. However, it has been repeatedly pointed out that most theories and explanations in biology cannot be accounted for in terms of laws and logical derivations (Hull 1979; Rosenberg 1985; Sober 1993), but are best characterized as descriptions of productive mechanisms (Bechtel and Abrahamsen 2005; Machamer, Darden, and Craver 2000; Skipper 1999; Wimsatt 1976). Given this shortcoming, Lindley Darden articulated a mechanistic version of the 'explanatory extension' thesis, more readily applicable to explanations in biology. Darden argues that

> [t]he general knowledge in molecular biology is best characterized not in terms of laws or a theory but as a set of mechanism schemas [where a] mechanism schema is a truncated abstract description of a mechanism that can be easily instantiated by filling it with more specific descriptions of component entities and activities. (2006, 111-112)

Building on this new approach, Darden (2006, 98) argues that classical genetics and molecular biology elucidate "separate but serially connected mechanisms." According to this account, Mendel provided a highly schematic outline of a series of events explaining inheritance phenomena. Then, classical genetics elucidated in more detail some elements contained in this scheme (e.g., the mechanism of allelic segregation, explained by meiosis, and recombination, explained by chromosomal crossing-over) while relegating other elements to 'black-boxes' (the ability of alleles to replicate and determine phenotypes), thus providing a first incomplete general schema of a series of mechanisms. Finally, molecular biology gradually filled in the remaining 'black-boxes' with more and more mechanistic details (most famously, the mechanisms of DNA replication and gene expression), until the present-day picture of genetics emerged. The 'serially connected mechanisms' account specifies the aspects of inheritance explained by classical genetics and those explained by molecular biology, and shows how the mechanisms postulated

by classical and molecular explanations fit together without leaving gaps in the productive continuity from start (the genotype of the parents) to finish conditions (the expression of specific traits in the offspring).

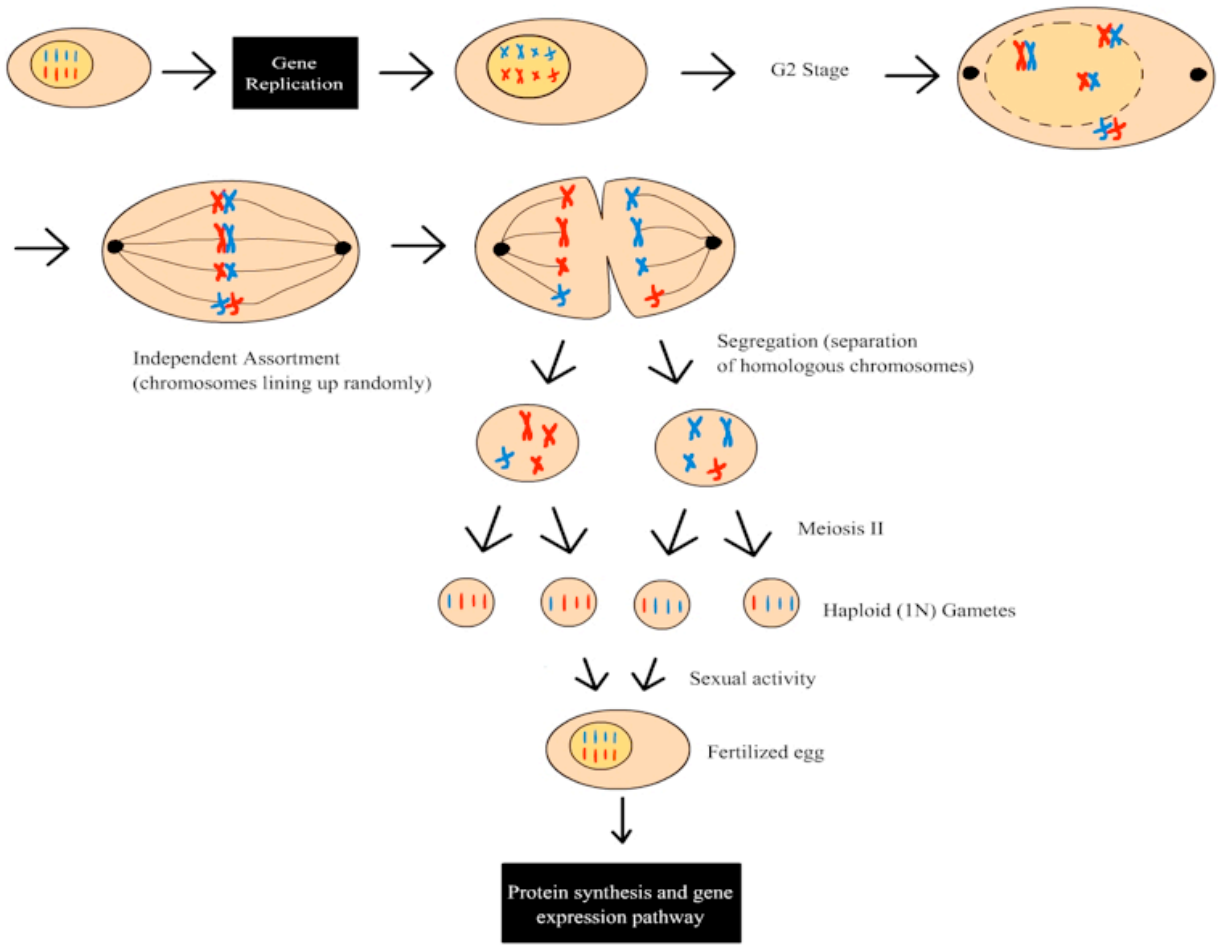

Fig. 1. Explanatory extension as serially connected mechanism schemas
[from (Darden 2006), used with permission]

While the 'serially connected mechanisms' account provides an adequate description of the relationship between classical genetics and molecular biology, it fails to explicitly address a major point of disagreement between reductionists and antireductionists: Does the elucidation of molecular details impose revisions of classical explanations? If the 'explanatory extension' thesis is true, then the intuitive answer is "No." Indeed, Hull (1974) and Kitcher (1982; 1989) suggest that the elucidation of molecular details must be neutral in respect to individual classical explanations: the molecular details contribute to a better understanding of aspects of inheritance not explained by classical genetics, but they do not provide a better explanation of the

transmission patterns already explained by classical explanations. While tempting, this answer is incorrect. In this paper, I discuss examples of 'explanatory interference', that is, cases when the accommodation of data from molecular biology results in a more precise genotyping and more adequate classical-style explanations of the transmission patterns associated with certain inherited conditions. Such examples constitute a problem, since they seem to contradict the 'explanatory extension' thesis and raise the possibility that a reductionist or eliminativist account might, after all, provide a better account of the relationship between classical genetics and molecular biology.

This paper has two aims. First, I identify instances of 'explanatory interference' in contemporary research practice. This is an important achievement, since, despite vigorous debates in the past, it has never been conclusively shown that the elucidation of molecular details impacts specifically on the empirical adequacy of classical explanations dealing with issues of transmission. Second, I show that both the 'serially connected mechanisms' account and instances of 'explanatory interference' can be accommodated without contradiction. To this end, I propose a new way of analyzing the relationship between classical genetics and molecular biology hinging on the properties of mechanism schemas, which can be completed, on the one hand, by elucidating some or all of the remaining 'black boxes' and, on the other, by instantiation via the filling-in of phenomenon-specific details. This result has implications for the reductionism-antireductionism debate since it shows that molecular elucidations have a positive impact on classical explanations, yet does not entail the reduction of classical genetics to molecular biology.[1]

The paper is organized as follows: In section 2, I review presently available answers to the question "Do molecular elucidations have a positive impact on classical explanations?" In section 3, I proceed to show that molecular elucidations have in fact a positive impact on classical-style explanations. In section 4, I provide a solution to the apparent incompatibility between the 'explanatory extension' thesis underlying the 'serially connected mechanisms' account and instances of 'explanatory interference' demonstrated in actual scientific practice.

[1] In response to initial attempts to model the relationship between classical genetics and molecular biology as a form of inter-theoretical reductionism, it has been convincingly argued that such a form of reductionism is not something biologists are actively interested in achieving (Darden 2006, 105-105; Schaffner 1974; 1993, 512; Waters 2008, 249).

Finally, in section 5, I summarize my arguments and discuss implications for the reductionism-antireductionism debate in genetics.

2. Do molecular elucidations have a positive impact on classical explanations?

The issue of reductionism in genetics takes, in part, the form of a debate about whether the elucidation of molecular details requires a revision of previously accepted classical explanations. In Alex Rosenberg's words, antireductionism is the claim that

> nonmolecular biological explanations are adequate and need no macromolecular correction, completion, or grounding. (2007, 120)

All parties agree that molecular biology elucidates the lower-level mechanistic and structural details of the entities and activities hypothesized by classical explanations. Furthermore, both reductionists and antireductionists acknowledge the causal relevance of the molecular structures and mechanisms underlying cytological, developmental and other higher-level biological phenomena. For example, nobody is denying that a phenomenon such as recombination is explained at the cytological level by chromosomal crossing-over, itself explained at the molecular level by a mechanism involving Spo11-mediated double-strand DNA break followed by the formation of a Holliday junction [for a more detailed example and philosophical discussion, see levels of mechanisms (Craver 2007, chap. 5)]. Rather, the disagreement is about the explanatory relevance of the molecular details to already successful nonmolecular explanations. Thus, the question is "Does the elucidation of the molecular mechanisms underlying cytological entities and activities contribute to the ability of classical genetics to provide more adequate explanations of the transmission of inherited traits phenomena?"

Several attempts to assess the impact of molecular elucidations on classical explanations have been made during exchanges between reductionists and antireductionists, yet no definitive conclusion was ever reached. Kitcher (1984) claims that taking into account the molecular details muddles the crispy-clear explanations of classical genetics, while Rosenberg (1985, 101) sees an unbridgeable degree of complexity separating classical and molecular explanations. In both cases, the argument is that molecular analysis reveals a multiplicity of interacting and redundant gene products involved in the production of any single phenotype, while transmission genetics explains the same phenotype more simply and elegantly by assigning it a small number of alleles

associated with a single locus. The argument is however rather vague, as no particular examples are discussed in thorough scientific detail. Equally problematic, the argument hinges on an alleged virtue of simplicity which, as I will show, is not reflected in the views and results of prominent geneticists such as T. H. Morgan or S. Benzer. Finally, neither Kitcher, nor Rosenberg discusses the possibility that taking into account molecular details sacrifices simplicity in favor of a much more valuable increase in empirical adequacy.

In his more recent work, Rosenberg claims that

> [m]olecular information about the location and structure of the genetic material [...] helps the Classical geneticist understand where Mendel's 'laws' go wrong, and what exceptions to these rules of thumb are to be expected. (1997, 447)

He concludes that

> molecular biology shows why Classical genetics is a useful instrument, even pedagogically indispensable, but is fundamentally flawed. (1997, 447)

It can be retorted though that Mendel's laws were corrected not so much by molecular biology, but within classical genetics itself after the discovery of linkage, recombination and complementation. Furthermore, claiming that classical genetics is 'fundamentally flawed' doesn't sit well with the generally accepted view that classical genetics offers satisfactory explanations of certain aspects of inheritance.

Kenneth Waters (1990, 132-133) argues against Kitcher that knowledge of the molecular mechanisms underlying chromosomal crossing over must somehow contribute to our understanding of inheritance. This must be indeed the case, but the claim is too general to conclude something specifically restricted to the impact of molecular elucidations on classical explanations. More recently, Waters adopts a different approach to the reductionism-antireductionism debate. He argues that

> [t]he developments following Watson and Crick's discovery that mattered were not primarily theoretical. [...] What changed biology so dramatically was a retooling of the investigative strategies used in genetics. (2008, 239)

The example discussed (a RNAi knockout study) shows how molecular biology provides additional means of experimental investigation and control in the context of a classical-style

(forward) genetic analysis. Waters is making a valid point, but this cannot be the whole story. As it stands, his account seems to entail that molecular biology is nothing but a set of experimental techniques and not a scientific field proper, endowed with its own theoretical and experimental resources. This is a counterintuitive conclusion that very few biologists would endorse. Furthermore, even if the contribution of molecular biology is primarily experimental, it is still not clear how the knowledge generated by classical and molecular techniques fits together. Do the two sources of information complement each other by providing knowledge about distinct aspects of the phenomena under study? Or do they make claims about the same aspects, and therefore there is a possibility that contradictions may arise? These questions remain unanswered.

3. Mendelian errors and molecular genotyping

My answer to the question "Does the elucidation of molecular details have an impact on classical explanations?" is "Yes." The key element in understanding how molecular elucidations can have an impact on classical explanations rests on the notion of 'schema instantiation.'[2] For example, the 'Central Dogma' is an abstract mechanism schema highlighting the common elements of the mechanisms responsible for prokaryotic and eukaryotic gene expression in general.

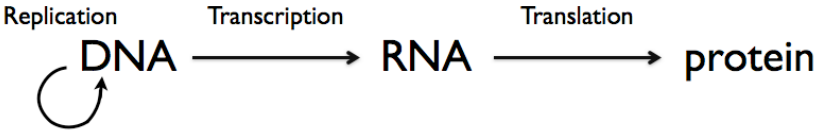

Fig. 2. The Central Dogma of molecular biology

However, if it is generally understood that genes determine phenotypes via a universal mechanism of gene expression involving transcription and translation, molecular explanations of individual phenotypes require the elucidation of many further details, such as the DNA sequences involved, the mechanisms regulating the expression of these sequences and the

[2] Kitcher (1989) proposed that general knowledge in science consists of 'schematic arguments' (sequences of 'schematic sentences' in which some nonlogical expressions are replaced with dummy letters) that can be instantiated by means of a set of 'filling instructions' for each term of the schematic argument. In the case of mechanistic explanations, Darden (2006) argues that general knowledge is best described as a set of mechanisms schemas, often represented via diagrams, that can be instantiated by filling it with specific descriptions of component entities and activities.

mechanisms by means of which the expressed gene products contribute to the phenotype under investigation. In other words, in order to provide a satisfactory explanation of the genetic underpinnings of any given trait, the 'Central Dogma' schema needs to be instantiated by elucidating and filling in phenomenon-specific details.

A similar comment applies to classical genetics. The Machamer-Darden-Craver (2000) characterization of mechanisms is compatible with the notion that classical genetics offers a general schema explaining the transmission of inherited traits by appealing to the segregation and recombination of alleles located at specific chromosomal loci (see Fig. 1). However, this schema too needs to be instantiated before it can account for the peculiarities of any given inheritance phenomenon. To give a very striking example, as early as 1911, Morgan discovered the complementation of the white and pink eye mutants in Drosophila (Morgan 1911). Complementation refers to a situation whereby the crossing of two different kinds of homozygous recessive mutants yields a wild-type phenotype (Lewis 1951; Benzer 1955). Classical geneticists interpreted complementation as an indication that the two mutations affect two distinct 'genetic units', dubbed 'functional units.' If the mutations were in the same unit, then the offspring could not have received a copy of the wild-type unit since none of the parents had one to begin with. This immediately indicates that, in many cases, more than one functional unit is required for the expression of any given phenotype. Furthermore, mutations targeting apparently unrelated traits can complement, meaning that mutation in one gene can affect several traits/biological functions. Finally, since non-complementing mutations can map at distinct chromosomal loci it is possible to distinguish between mutations in the same functional unit that result in an identical phenotype, meaning that classical geneticists were able to distinguish mutations that cannot be directly differentiated by observing phenotypes before DNA sequencing techniques became available. This indicates that the general schema postulating segregation and recombination of alleles located at specific chromosomal loci provides only the rough guideline for a genetic explanation. A considerable amount of further research is required in order to work out genetic maps capable of accounting for every single instance of linkage, recombination and complementation associated with the specific transmission patterns under investigation.[3]

[3] The discovery of complementation also shows that the simplicity advertised by Kitcher (1984) and Rosenberg (1985, 101) dissolves away in the kind of complexity typically associated with molecular analysis. By the same

Since schema instantiation is dependent on further information, it becomes interesting to investigate the nature (experimental data vs. theoretical assumptions) and origin (the theory's own internal vs. external theoretical and experimental resources) of this information. In the case of classical genetics, genes can be identified via classical techniques involving analyses of linkage and complementation (or cis-trans) assays; this strategy relies on the internal resources of classical genetics and can be referred to as intra-theoretical schema instantiation. Alternatively, genes can be identified as transcription units characterized by the presence of structural motifs (e.g., TATA box followed by an open reading frame) and homology with known gene product sequences (Altschul et al. 1990; Wain et al. 2002); this strategy relies on the external resources of molecular biology, and can be referred to as cross-theoretical schema instantiation. Cross-theoretical instantiations of the general explanatory schema of classical genetics are possible because loss of function mutations in the regulatory and coding sequences of distinct transcription units required for the synthesis of gene products involved in the same metabolic or signal transducing pathway complement each other. Hence, transcription units identified via molecular techniques behave like classical functional units. Furthermore, transcription units were shown to overlap extensively with functional units, as mapped via classical analysis (Benzer 1966; Mosig and Eiserling 2006).

Next, since the same general schema can be instantiated intra- and cross-theoretically, it becomes interesting to establish whether the two instantiations coincide, or whether they conflict with each other. If conflicts arise, it is important to find out how they are settled. In the case of classical genetics, it can be shown that taking into account theoretical assumptions and experimental data from molecular biology force distinct, and usually more complex, schema instantiations. Furthermore, such cross-theoretical instantiations are typically more adequate than straightforward intra-theoretical instantiations relying solely on the internal resources of classical genetics.

Let us imagine that a particular metabolic pathway involves three enzymes E1, E2 and E3. Given this piece of information from biochemistry, it becomes reasonable to hypothesize that at least three distinct genes must be expressed. Let us further assume that G_{E1}, G_{E2} and G_{E3} are then

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token, Rosenberg's (1997, 447) argument that classical genetics is false because nothing in the physical world corresponds to its level of simplicity is also considerably weakened.

identified as alleles encoding functional products, while alternative alleles M_{E1}, M_{E2} and M_{E3}, naturally occurring or created in the lab, encode mutated, non-functional products. In order for the normal/wild-type phenotype N_{Ph} to obtain, an organism must have at least one copy of the genes G_{E1}, G_{E2} and G_{E3} (in classical terms, the wild-type allele is dominant). A mutant phenotype M_{Ph} obtains when at least one gene is mutated on both chromosomes (the mutant allele is recessive). Consider now that G_{E1} is never mutated in the populations accessible to classical analysis and that G_{E2}/M_{E3} and M_{E2}/G_{E3} fail to complement because, it turns out, their respective products E2 and E3 form a functional hetero-dimer.[4] If a geneticist ignores these details from biochemistry and molecular biology, he or she ends up identifying a single gene required for normal metabolism and concludes that two alleles of the same gene are associated with metabolic function and dysfunction. This is a case when intra-theoretical schema-filling diverges from cross-theoretical schema-filling. One gene or three, the general explanatory scheme remains the same. However, in this hypothetical case, theoretical assumptions justified by a partial elucidation of the metabolic pathways underlying the phenotype under investigation [i.e., the one-enzyme one-gene assumption (Beadle and Tatum 1941)] prompts a distinct schema instantiation that does not coincide with the simpler one favored by straightforward classical analysis.

Subtle, yet measurable differences in symptoms and responses to treatment always puzzled clinical geneticists. Simplified genotypes provide adequate explanations only by ignoring a host of minute variables, such as the severity of the symptoms, the onset of the disease, secondary complications, and differences in response to treatment. In contrast, a more minute analysis taking into account the molecular details is often able to account for the diversity of sub-phenotypes. A famous example is that of Huntington disease. Classical analysis notoriously failed to explain why 5% of the individuals inheriting the dominant allele for Huntington don't develop the disease while the remaining 95% are affected to various degrees (in classical terms, the allele is said to be partially penetrant and to display various degrees of expressivity). In contrast, the molecular analysis reveals that the affected gene (HTT) contains multiple repeats of the CAG sequence, coding for glutamine. The normal gene codes for less than 27 glutamine amino-acid repeats, while the mutated version codes for 36 or more (Kieburtz

[4] Two peptide chains, coded by distinct genes, combining to form a single functional protein; in such cases complementation experiments were shown to be inconclusive (A. Garen and S. Garen 1963).

et al. 1994). The number of additional glutamines in the final gene product is related to the rate of neuronal decay, and thus to the severity of the symptoms (Chong et al. 1997). As it turns out, it is not the case that a single allele displays different degrees of penetrance and expressivity; instead, a whole series of mutations is responsible for the variability of the observed symptoms (Fig. 3). The molecular instantiation provides a more satisfactory explanation both from an empirical adequacy point of view, as well as by avoiding giving metaphysical weight to the purely hypothetical properties of 'penetrance' and 'expressivity.' Note also that, for the time being, the mechanism underlying the disease, as well as the function of HTT, are not fully understood. The molecular analysis does not elucidate the 'black box' mechanism linking genotype and phenotype. Rather, it provides a more adequate 'classical-style' characterization of the genotype associated with the disease and its transmission patterns.

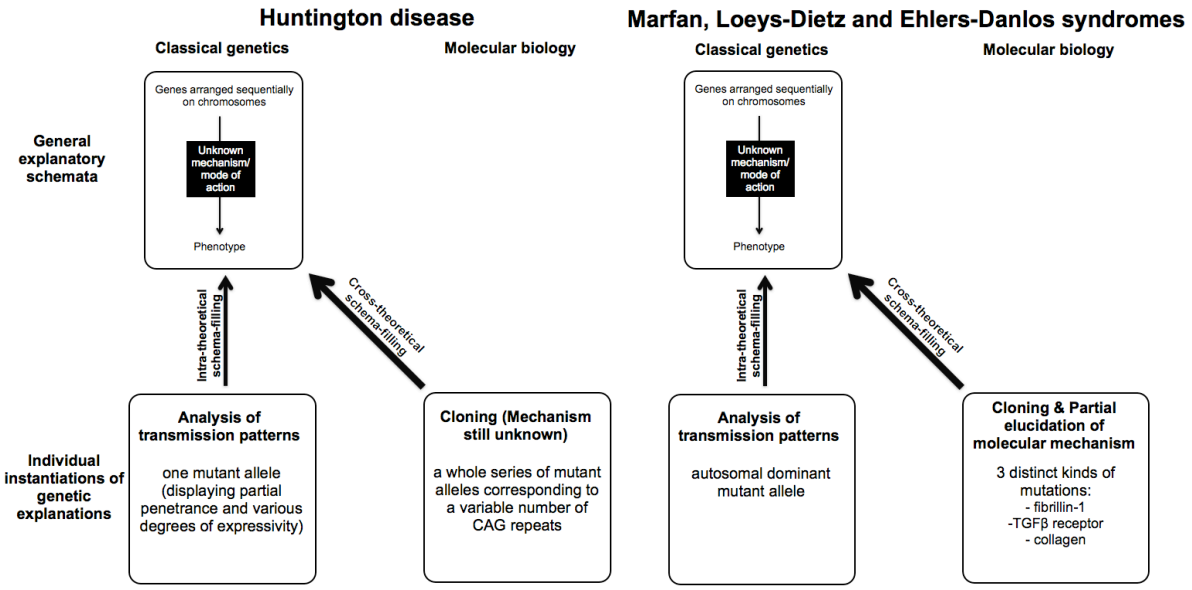

Fig. 3. Alternative, intra- vs. cross-theoretical schema instantiations in classical genetics
(the arrows indicate the import of specific details into the general schema of classical genetics)

Subtle differences between the postulated genotypes also make an important difference when it comes to providing accurate predictions of offspring phenotypic frequencies required for medical applications such as genetic counseling. A very striking example where a more complex genotype resulting from cross-theoretical schema filling is more adequate than the simpler genotypes resulting from straightforward intra-theoretical schema filling is that of Marfan, Loeys-Dietz and Ehlers-Danlos syndromes. Since they are all autosomal dominant diseases characterized by similar symptoms, they were, and still are often confused as a unique genetic disease. It turns out Marfan syndrome is caused by mutations in the fibrillin-1 gene, coding for a

glycoprotein found in the extracellular matrix. Although the exact mechanism of the disease is not known, the favored explanation is that fibrillin-1 binds TGFβ (known to inhibit cell growth and induce apoptosis) keeping it inactive; dysfunctional or reduced levels fibrilin-1 result in a TGFβ-induced inflammatory reaction leading to connective tissue degradation (Pereira et al. 1999). In contrast, Loeys-Dietz syndrome is caused by mutations in the TGFβ receptor genes resulting in enhanced TGFβ signaling (Loeys et al. 2005). Finally, the Ehlers-Danlos family of syndromes is due to mutations that affect the structure or production of collagen [reviewed in (Beighton et al. 1998)]. It follows that TGFβ receptor inhibitors may help alleviate the symptoms of Marfan, but not those of Loeys-Dietz and Ehlers-Danlos syndromes. Targeting intracellular components of the TGFβ signaling pathway may provide a cure for the Loeys-Dietz and Marfan syndromes, but should have no impact on patients affected by Ehlers-Danlos syndromes. Finally, gene therapy targeting the collagen genes may provide a cure to the Ehlers-Danlos family of syndromes, but are expected to be ineffective in treating the Marfan and the Loeys-Dietz syndromes. An empirically adequate explanation must explain such minute clinical differences. In this respect, the simpler explanation postulated in light of the classical analysis (i.e., mutations in one gene are responsible for one disease) is less adequate than the more complex explanation taking into account partial knowledge from molecular biology.

In the above examples, a partial elucidation of the molecular details prompts a revision of the genotypes underlying the inherited condition. A revision of the genotype counts as an instance of 'explanatory interference' because it prompts a further revision of the predictions made by classical-style explanations (e.g., the patterns of transmission associated with that condition). Since these revisions result in a better empirical fit (e.g., explain the spectrum of phenotypic differences associated with Huntington disease), more satisfactory explanations (e.g., dispense of the notions of 'penetrance' and 'expressivity') and an ability to explain potential anomalies (e.g., differences in response to treatment), I conclude that the elucidation of the molecular details has a positive impact on classical explanations.

4. An alternative approach to reductionism-antireductionism debate in genetics

If molecular elucidations have a positive impact on the empirical adequacy of classical explanation, does this mean that classical genetics reduces to or is replaced by molecular

biology? The reductionism-antireductionism debate in genetics hinges, in part, on the issue of 'explanatory extension' vs. 'explanatory interference.' Some philosophers of biology (Hull 1974; Kitcher 1984) rejected reductionism on the grounds that molecular biology explains aspects of inheritance not explained by classical genetics and, therefore, the elucidation of molecular details shouldn't affect classical explanations. Paradoxically, this claim is falsified by the discussed examples, yet reductionism is by no means vindicated. Reductionism posits a stronger thesis, summarized by Waters as follows:

> Watson and Crick's discovery [...] led to a deeper and more fundamental, molecular-level theory. The new theory allegedly improves upon higher-level explanations of the classical theory by explaining its core theoretical principles in terms of molecular processes. (2008, 239)

Even if the examples discussed in this paper show that classical explanations need corrections and are enhanced by taking into account molecular elucidations, terms like 'meiotic segregation', 'recombination' or 'complementation' are not recast in molecular terms. Nor does there seem to be any motivation for such a recasting. Data from molecular biology are used to identify functional units, which are classical gene concepts [genes as 'difference makers' (Griffiths and Stotz 2007; Rheinberger and Müller-Wille 2008; Waters 1994)] and provide the basis for classical-style explanations concerned with transmission and not the mechanisms linking phenotype and genotype (Morgan 1935; Moss 2003; Waters 2004). It seems therefore safe to conclude that despite the improvements brought about by molecular biology, the general explanatory schema of classical genetics is not derived, inferred or reconstructed in any way from biochemistry or molecular biology.

The solution to this paradoxical situation whereby classical genetics doesn't seem to reduce to or be replaced by molecular biology, yet there is a clear sense in which molecular biology represents an improvement over classical genetics lies in the peculiarities of mechanism schemas. According to the 'serially connected mechanisms' account, the 'black-boxes' of the general schema of classical genetics are elucidated in order to generate the general explanatory schema of molecular biology. This is a form of inter-theoretical schema-filling accounting for the 'explanatory extension' aspect of the relationship between classical genetics and molecular biology. At the same time, the same general schema of classical genetics is also instantiated by

filling in phenomenon-specific details in order to generate individual explanations of inheritance phenomena. This can be achieved intra-theoretically, by using the internal resources of classical genetics; or cross-theoretically, by taking into account data and assumptions from molecular biology (Fig. 4).

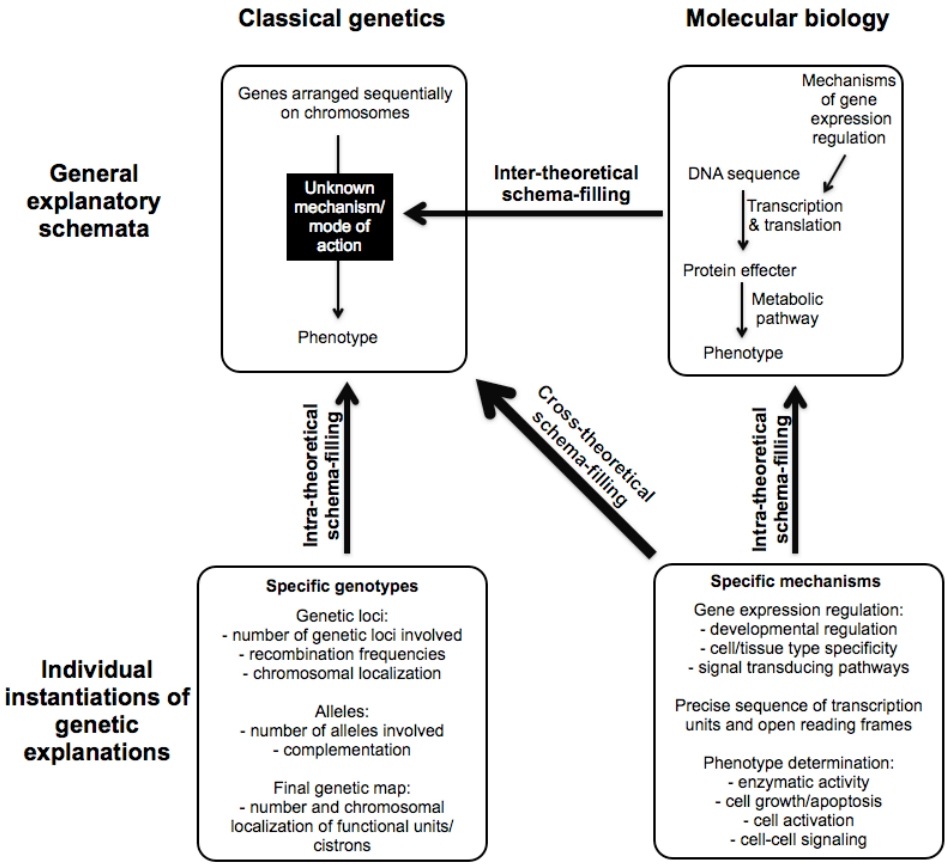

Fig. 4. Inter-, intra- and cross-theoretical schema-filling

As exemplified in the previous section, there can be a clash between intra- and cross-theoretical schema instantiation, typically resolved in favor of a cross-theoretical instantiation taking into account molecular findings. However, this clash has no bearing on inter-theoretical schema-filling and the 'explanatory extension' aspect of the relationship between classical genetics and molecular biology. Inter-theoretical schema-filling is about elucidating the 'black boxes' of the general schema of classical genetics, while intra-/cross-theoretical schema-filling is a matter of instantiating individual explanations by filling in the details specific to a particular inheritance phenomenon.

5. Conclusion

In this paper I argue that the details of a general mechanism schema can be completed:

(i) inter-theoretically, by elucidating some or all of the 'black boxes' of a previous general explanatory schema in order to generate another general explanatory schema, as illustrated by Darden's 'serially connected mechanisms' account of the transition from classical genetics to molecular biology (horizontal bold arrow at the top of Fig. 4);

(ii) intra-theoretically, by filling in phenomenon-specific details using the theory's own internal theoretical and experimental resources in order to instantiate individual explanations of particular phenomena (vertical bold arrows in Fig. 4); and

(iii) cross-theoretically, whereby theoretical and experimental considerations from one theory contribute specific details required for the instantiation of individual explanations derived from another general explanatory schema without explicitly elucidating any of the 'black boxes' of the latter (diagonal bold arrow in Fig. 4).

Distinguishing between the three types of schema-filling is crucial for a clear understanding of the complex relationship between classical genetics and molecular biology. As expounded by Darden (2006), and on occasions by Kitcher (1982; 1999), the 'explanatory extension' thesis is a claim about inter-theoretical schema-filling. In as much as molecular biology elucidates the 'black boxes' of the general schema of classical genetics, the relationship between the two sciences is neither reductive, nor eliminative, but rather a form of cumulative completion. To this day, genetics combines classical experimental and explanatory strategies, such as breeding and genetic linkage mapping of phenotypes, with cloning, sequencing and reverse genetic analysis later introduced by molecular biology (Falk 2003; Vance 1996; Waters 2008). Furthermore, the fact that experimental data and theoretical assumptions from molecular biology have a positive impact on classical-style explanations hints to a high level of integration of the two sciences in a unique field of research. In these respects, the transition from classical genetics to molecular biology is theoretically-cumulative, ruling out reductionism in favor of inter-field integration (Darden and Maull 1977; Darden 2006). Finally, since classical genetics and molecular biology provide explanations at different levels of organization (e.g., cytological vs. molecular), claims to a 'mosaic' of multilevel explanations in biological sciences (Craver 2007) are also vindicated.

In contrast, according to a non-integrative brand of antireductionism held sometimes by Kitcher (1984) and identified by Rosenberg (2007) as defining antireductionism in biology, molecular biology fails to contribute in a positive way to the ability of classical genetics to provide adequate explanations of inheritance phenomena. This thesis is a combination of the 'explanatory extension' thesis doubled by the claim that classical genetics generates its most successful explanations in virtue of intra-theoretical schema instantiation, while 'explanatory interference' from molecular biology (cross-theoretical instantiation) is impossible, irrelevant or damaging. If this is how antireductionism is construed, then antireductionism is false. I showed by means of examples that data from biochemistry and molecular biology needs to be accommodated by changes in genetic explanations resulting in a more precise genotyping. In turn, a more accurate knowledge of genotypes plays an important role in making more accurate predictions of phenotypic distributions, assessing the risk of disease and response to treatment, providing more accurate diagnosis and genetic counseling.

In order to resolve the apparent problem, I argued that instances of 'explanatory interference' do not conflict with the 'explanatory extension' aspect of the relationship between classical genetics and molecular biology as long as a distinction is made between two distinct degrees of abstraction. At the degree of abstraction associated with the general explanatory schemas of classical genetics and molecular biology, molecular biology extends classical genetics by elucidating some of its 'black boxes' (inter-theoretical schema-filling). In contrast, at the level of specific instantiations associated with individual explanations, data from molecular biology can and often is used to fill-in phenomenon-specific details (cross-theoretical schema-filling). As exemplified in the paper, taking into account the molecular details results in more adequate explanations.

Although this complex issue transcends the more modest scope of this paper, I would like to conclude with a few words on the possible implications for the connection between causation and explanation. The 'explanatory extension' aspect of the relationship between classical genetics and molecular biology indicates that not all causally relevant factors are necessarily deemed explanatory relevant. For most philosophers, this conclusion is hardly a surprise. What may come as a surprise is that the explanatory relevance of causally relevant factors seems to be context-sensitive. At the degree of abstraction associated with general explanatory schemas, the molecular details (e.g., the molecular mechanisms underlying chromosomal crossing-over) are

acknowledged to be causally relevant for the production of inheritance phenomena, with all that this may entail in terms of experimental manipulability and practical applications, yet their elucidation did not prompt a rethinking of previously accepted classical explanations (e.g., recombination as an explanation of certain anomalies in offspring phenotypic frequencies). However, as shown in this paper, at the level of particular instantiations of classical-style explanations, some molecular details become highly relevant.

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