

## 9. Too Many Kinds of Genes? Some Problems Posed by Discontinuities in Gene Concepts and the Continuity of the Genetic Material (1995)<sup>1</sup>

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Broadly speaking, there are two kinds of gene concepts. In this brief chapter I will offer a modest account of each. I seek to show that both are legitimate and that it is necessary to understand their interplay in order to understand the history of genetics and a number of current issues in genetics. I argue that the first kind of concept makes sense of the conceptual continuities in the history of genetics, but yields concepts that are too generic or schematic to specify adequately what is referred to by *'the'* gene concept and allied concepts. I will show that we cannot do without such generic or schematic concepts. Indeed, without schematic concept(s) of the gene, there would be no such discipline as genetics, but, without supplementation by more specific gene concepts the schematic concepts do not suffice for specifying the reference of the term 'gene' – indeed, they do not specify what genes are well enough to ensure that the term refers successfully at all. In less philosophical language, these schematic concepts are impotent to specify exactly what we are talking about when we talk about genes. The second kind of gene concept, in contrast, yields specific gene concepts, but does so at the price of conceptual discontinuity. I shall argue that if one restricts oneself to the series of discontinuous gene concepts, the findings of molecular genetics favor abandoning a univocal and specific concept of the gene altogether in favor of a pair of concepts – the concept of genetic material plus that of the expression of genetic information. I will even suggest that, without the schematic concepts, molecular genetics would be well served by abandoning specific gene concepts with a concept of the genetic material. As some other contributors to the workshop in which this chapter was originally presented have argued,<sup>2</sup> the information content of the genetic material is extremely dependent on the cellular or subcellular context in which it is expressed. This provides one of the rationales for suggesting that molecular biologists could abandon specific concepts of the gene, deploying, instead, concepts focusing on the continuous genetic material and the controls governing what is still called gene expression.

### Schematic Gene Concepts

Any science that seeks to locate hidden causes of some spatio-temporally delimited class of phenomena must use indefinite descriptions.<sup>3</sup> These are descriptions that leave the

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<sup>1</sup> This text is revised from a paper presented to a workshop on gene concepts at the Max Planck Institute for the History of Science in Berlin in 1995. I am grateful to the discussants at that meeting for criticisms and suggestions. The content of the chapter has not been adjusted to take subsequent developments into account.

<sup>2</sup> After a follow-up workshop at the Max Planck Institute, most of the papers alluded to were published in (Beurton, Falk and Rheinberger 2000). The papers by Falk, Fogle, Gifford, Gilbert, Holmes, Rheinberger, and Schwartz are particularly relevant to this chapter.

<sup>3</sup> I first learned the importance of indefinite descriptions in my graduate studies with Wilfrid Sellars. The concept of the reference potential of a concept, deployed in Chapter 7 is, in some respects, a development of one aspect of the indefinite reference of schematic gene concepts.

exact referent of a term open. An example would be a Mendelian description like ‘*the factor, whatever it is, in the germ cells of these peas that causes them to produce plants that are shorter than the tall plants produced from peas from the same pod*’. Such specifications are indefinite in not adequately specifying what the causal factor in question is or even what category or sort of thing or process the factor is. Indefinite descriptions can genuinely refer to entities, as, indeed, the example I just gave, used in the right circumstances does, but they can also be associated with seriously false descriptions or commitments. This is illustrated by the view, common before the middle of the twentieth century that Mendelian factors (or genes) are composed of proteins. Mendelian genetics, taken strictly (i.e., without commitment to the localization of genes on chromosomes), used gene concepts based on very open-ended indefinite descriptions of exactly the form illustrated above.<sup>4</sup>

I call concepts like that of a gene thus understood *referentially indefinite causal (or functional) concepts*. In particular, the identification of a gene illustrated above is indefinite, but is accomplished in terms of a two part functional description. The first part specifies a difference in the phenotype of the organism bearing a gene (tall vs. short); the second requires a pattern of transmission of the factor(s) responsible for the change. (One can distinguish different genes affecting, say, a plant’s height or its flower color by their behavior in breeding experiments, by whether or not they ‘Mendelize’ or follow some recognizable variant of classic Mendelian patterns of inheritance.)

Here is a schematic formulation of a referentially indefinite functional gene concept: *A gene for trait x is any stably inherited factor that causes an organism [or certain cells of the organism], given the rest of what it has in common with conspecifics, to have the potential for manifesting x, where x will (or can be made to) appear under the appropriate developmental plus environmental circumstances.*<sup>5</sup> Distinct genes for x may exist and may be discriminated from each other either by specific differences in the

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[Added in 2003]: For amplification of my views along these lines, see the treatment of referentially open concepts in (Burian 2000, esp. §§ 3-4).

<sup>4</sup> Johannsen’s 1909 attempt at an a-theoretical definition (Johannsen 1909) illustrates the point precisely. In Carlson’s translation (Carlson 1966, pp. 20-22): “The word ‘gene’ is completely free from any hypotheses; it expresses only the evident fact that, in any case, many characteristics of the organism are specified in the gametes by means of special conditions, foundations, and determiners which are present in unique, separate, and thereby independent ways – in short, precisely what we wish to call genes.” Genes are thus the differences, whatever they may be, between gametes that cause organisms to have the potential for revealing patent, independently-heritable, traits. Darden (Darden 1991) amplifies this point usefully in firmly separating Mendelian genetics as developed after the ‘rediscovery’ of 1900 from the chromosomal theory developed by the Morgan group and others.

<sup>5</sup> It is important to note that as we develop an account of the relevant causal chains, we may come to adjust what we count as a trait or, at least, what we count as a trait caused in a particular, stably inherited, manner. Think, for instance, of the multiplication of distinct disease entities, e.g., some of the cancers formerly believed to be a single disease, as we have learned to distinguish different underlying ways in which, e.g., the regulatory apparatus of certain types of cells can be disrupted so as to yield phenotypically similar outcomes. It is also important to recognize that the schematic definition may require specification in a great variety of ways. Thus the specification of ‘modifier genes’ and ‘regulatory genes’ may have to be relative to a specific gene or control pathway carried by some, but not all, conspecifics for their.

phenotypes they cause or by demonstrating that they can be inherited independently of each other. Stadler (Stadler 1954) used the label ‘the operational gene’ for genes, thus indefinitely described. There were two points involved: first, there were competing theories, between which no decision was possible, of the constitution of operationally delimited genes. Second, breeding procedures allowed workers to distinguish between distinct genes with otherwise identical phenotypic effects.

Such concepts imply no direct claims about what genes *are*, e.g., what they are made of, or even whether they are chemical substances or stable harmonic resonances, which seems to be what Bateson thought they might be. Without independent knowledge of gene structure or composition, then, these concepts do not provide a fully adequate way of individuating genes. (For that reason, Stadler spoke pessimistically of our inability to resolve questions about ‘the hypothetical gene,’ in distinction to the operational gene.) If no information about structure or composition is built into the gene concept, it is not possible to count genes in a stably satisfactory way. This helps make sense of the fact that the chromosome theory – or something like it – was flatly needed to complement or complete Mendelian genetics. And it helps explain part of what is accomplished by the specification of genes as composed of DNA and RNA. But once such additional information is built into the concept of the gene, the theoretical presuppositions of gene concepts are radically strengthened – and, for most of the history of genetics, the presuppositions involved have been substantially false.<sup>6</sup>

One can view the history of genetics as involving, among other things, a series of attempts to obtain experimentally and conceptually sound ways of filling in indefinite descriptions of genes of the sort suggested above. What *should* count as a gene, given the indefinite starting point, depends on the specific traits or functions examined and the patterns of inheritance that they exhibit. It also depends on larger commitments as well, such as the means we employ in determining that something (e.g. a particular sequence of nucleotides), in context, is causally responsible for the trait differences in question. It depends, further, on the restrictions we place *in context* on the ascription of causal responsibility. In the century or so with which we are concerned, it has been at various times stoutly affirmed and stoutly denied that to count as a gene an entity had to be on, or to be a part of, a chromosome, or composed of protein, or composed of nucleic acid, and so on. In general there is no adequate way of telling when such claims were intended as

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<sup>6</sup> This claim is, of course, contentious, but I believe it is correct. Consider the sorts of substantially false conceptual commitments that have commonly been made: genes are discrete particles, genes are composed of proteins, they are located only on chromosomes, they are linearly contiguous, they are non-overlapping, etc. Please note that when one claims that such commitments of detail have been built into gene concepts and are substantially false one does not imply that genetics is based on fundamental mistakes. The ability to retreat to more generic concepts and the associated definitional muddiness to which Rheinberger refers in (Rheinberger 2000) allow for substantial conceptual falsity to coexist with a fundamentally sound theory or, better, a fundamentally sound program of research or research tradition yielding a sequence of improving theories. These considerations support one of Rheinberger’s contentions and work against another. In contrast to Rheinberger, I hold that we need concepts far more specific and less ‘dirty’ than is justified by available evidence. He is correct, however, that such meta-level concepts as *research programme* or *research tradition* also must be open textured in much the same way that the concept of the gene is if *our* account of the history and conceptual structure of genetics is to be workable.

conceptual and when they were intended as factual claims. For this and other reasons, to make sense of the history of genetics we need to understand that *when such commitments had conceptual force, there was always a pathway of retreat open*. The underlying concepts to which people retreated when necessary were referentially indefinite functional concepts.

It should be clear that indefinite descriptions of genes, even when conjoined with massive sets of experimental results, are not sufficient to specify exactly what terms like ‘gene’ or ‘gene for x’ and their cognates refer to. One thing that is often meant by a (or ‘the’) theory of the gene is the theory-based specification of what it is that goes into individuating genes beyond the indefinite descriptions plus sheer experimental findings. A great deal is involved here. Among them, for example, I include abstract principles for the delimitation of causes, the delimitation of the biological functions to be examined [cf. visible phenotypes vs. protein synthesis], and commitments about the material composition, structure, or location of genes that constrain the concept of a gene and the possible referents of that concept. To understand the historical continuities that make genetics into a discipline and give geneticists a series of problematics on which to work, it is necessary to recognize this role of referentially indefinite concepts, but also to recognize that referentially definite concepts (or, at least, referentially more definite concepts) are needed to specify *what genes are* and are needed to develop means of testing the principal claims made about them – claims about how to individuate them, how they act, and so on. The need to answer such questions has had considerable impact on the character of theory in genetics. Indeed, the failure to develop globally satisfactory definite descriptions of genes is part of what moves me to suggest the need for conceptual reform in molecular biology.

### **Discontinuous Gene Concepts**

More specific concepts of the gene, though they may still allow further specification, are committal, at least to some degree, about the structure or location of genes. What is typically required is a mixed mode of identification in terms of both structure and function. When such definite concepts embody false presuppositions they may, if taken literally, turn out not to refer to anything [e.g., when they make the mistaken commitment that genes are composed of proteins] or they may apply to a subclass of the entities currently considered to be genes in molecular biology [as do those gene concepts that require genes to be composed of DNA, which miss the genes of RNA viruses].

It is always possible to retreat to a less definite description of genes and to set as a constraint on successful use of the terms in question that they refer to a causal factor contributing to the occurrence of a well specified phenomenon. Of course, they might then end up referring to an integron (see Rheinberger 2000), and not DNA or RNA as such at all. Thus, it is (nearly) always possible to retreat from false presuppositions so that it is clear that the claims of scientists who employed those presuppositions made good sense (see above, chap. 7, plus Burian, Richardson and Van der Steen 1996, Kitcher 1978, 1982). But it is also true that to individuate genes one must specify, among the thicket of factors contributing causally to any functional state, the substrates out of which genes are built and the structures that can count as relevant causes (and thus deserve to be identified as genes). Note that for this class of gene concepts the choice of a phenotype is crucial in determining what counts as a gene; when the phenotype is an amino acid

sequence, genes will be individuated differently than when the phenotype is something like the suppression of the expression of certain other genes. And it will continue to be the case that biologists with different interests will seek genes for phenotypes of different sorts. Thus, one cannot escape the recognition that there are sharp discontinuities in the history of genetics – discontinuities that cannot be bridged directly [‘genes must be composed of protein’ vs. ‘genes must be composed of nucleic acids’]. Nonetheless, such differences can be bridged via a retreat to less definite descriptions.

Once this point is granted, it is clear that the findings of molecular biology, some of which I allude to briefly in the next section, are readily interpreted so as to call into question whether genes are particulate without preventing those of us who deny that they are particulate from referring to the same things that our forefathers in Morgan’s and Bateson’s groups did when they used terminology committed to particulate genes and dynamic equilibria respectively. Indeed, in light of the treatment of concepts already given, I suggest that the findings of molecular biology allow one to challenge the claims that the terminology of genes is well-defined and that it picks out a well-delimited group of entities. Given the range of functions for which we seek genes, one may even doubt whether all the gene-like causes are restricted to nucleic acids (cf. prions). But I set that issue aside so that we may deal with the question whether we have a good way of settling which parts of which DNA and RNA molecules ought to be considered to be genes in light of contemporary knowledge. To this question I believe that there is no systematically satisfactory answer. The best answer in a given case depends on our purposes and on the schemes of classification we employ, both of the functions that may be caused genetically and of nucleic acid molecules and their parts.

### **Continuities in the Genetic Material**

Within rather broad limits, we are free to use terminology as we choose, although it pays to be reasonably clear about our usage and not to cause needless confusion by using preempted terms in ways that conflict with common usage. The term ‘gene’ in molecular biology is a genuine accordion term – its expansion and contraction make for a lot of semantic music and allied quibbling. But the arguments involved are not always empty semantic quibbles, for they turn on the inclusion or exclusion of a number of genetic functions performed by nucleic acids that do not fit any of the standard structural constraints on genes. Underlying the different terminologies are serious disagreements about the status of parts of nucleic acid molecules that behave or are treated in different ways in different cellular contexts and at different phases of ontogeny. I cannot pursue these issues very far here (see chap. 12 for some further discussion), but will take up a few matters briefly. For convenience, I will work with one of the broader gene definitions (specifically, of eucaryotic genes) that I have encountered (Singer and Berg 1991).<sup>7</sup>

We define a [eucaryotic] gene as a combination of DNA segments that together comprise an expressible unit, a unit that results in the formation of a specific functional gene product that may be either an RNA molecule or a polypeptide. The DNA segments that define the gene include the following:

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<sup>7</sup> Chapters 11 and 12 contain illustrations that will help the reader unfamiliar with the technical terminology to understand Singer and Berg’s text.

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1. The transcription unit refers to the contiguous stretch of DNA that encodes the sequence in the primary transcript; this includes (a) the coding sequence of either the mature RNA or protein product, (b) the introns, and (c) the 5' leader and 3' trailer sequences that appear in mature mRNAs as well as the spacer sequences that are removed during the processing of primary transcripts of RNA coding genes.
2. The minimal sequences needed to initiate correct transcription (the **promotor**) and to create the proper 3' terminus of the mature RNA.
3. The sequence elements that regulate the rate of transcription initiation: this includes sequences responsible for the inducibility and repression of transcription and the cell, tissue, and temporal specificity of transcription. These regions are so varied in their structure, position, and function as to defy a simple inclusive name. Among them are **enhancers** and **silencers**, sequences that influence transcription initiation from a distance irrespective of their orientation relative to the transcription start site (pp. 461-462, see also pp. 435 ff. and 457 ff.).

This definition includes a great deal that others would exclude. A more orthodox definition, like that of (Goodenough and Levine 1974, 291) would restrict the gene to those nucleotides which, “when transcribed, will produce a biologically active nucleic acid,” thus excluding promotor sites, enhancers, silencers, introns, and the like. But no matter: on either definition most eucaryotic genes are discontinuous stretches of continuous DNA, since introns are excised from biologically active RNAs. Worse yet, in many eucaryotes and quite a few prokaryotes, chain termination is dependent on physiological circumstances and/or is developmentally regulated. This means that the size of a gene – or what parts of the DNA of a multigene family function as genes rather than counting as pseudogenes – depends on physiological circumstances or developmental stage. Worse yet are the cases in which there is partly programmed, partly random gene shuffling during ontogeny or in response to SOS signals. I cite mammalian immune systems and the rec-A system of *E. coli* and related systems in other bacteria as examples. Such shuffling of the genetic material means that the genetic contents of a zygote (i.e., a fertilized egg) are not preserved in certain somatic cell lineages or even (in some cases) passed along to the offspring of fissioning bacteria. The dynamism of the genome is of great importance for the definitional and conceptual issues that belong at the heart of this paper.<sup>8</sup>

It might be thought that this argument can easily be interpreted as a trivial semantic argument about how we should define terms, and not as an argument bearing on how we should think about genes in light of the findings of molecular biology. The purpose of the next argument is to show that the issues just raised are not merely semantic in this pejorative sense, but seriously affect our interpretation of the history of genetics and impinge on how biologists should be thinking at this point. The moral that I wish to draw is that we should think, not of “the molecular biology of the gene” [to use a well known title (Watson 1965)], but of the “molecular biology of the genetic material.”

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<sup>8</sup> [Added in 2003:] For recent reviews providing some details and amplifying on the importance of such issues, see (Fogle 2000, Portin 2002).

(I have taken this phrase from somewhere, but I am no longer quite sure where – I believe I owe it to Dan Hartl.)

The argument is centrally concerned with the continuity of the genetic material: The intermediate conclusion which I will draw is this: An examination of intrinsic features of RNA or DNA is not sufficient for the task of delimiting which parts of these molecules, or which molecular structures, should count as genes. The principal reason for this is very simple – context dependence.<sup>9</sup> Ask what bits of DNA or RNA perform functions that we wish to identify as genetic. It takes an enormous amount of machinery for genes to be expressed. There is a huge number of processing steps, nearly any one of which, in context, can affect the times and places at which informational molecules yield products – and just which products they yield. It was known as early as 1987 that the translational apparatus alone requires some 200 macromolecules (Freifelder 1987, p. 367)! Corresponding to the richness and variability of the mechanisms involved, is the richness of the alternative results (even at the molecular level) when a given stretch of nucleic acid is transcribed or enters into an interaction of some sort. The answer to the question *which stretches of nucleic acid should count as genes* depends not only on the functions and the sequence of nucleotides involved we have chosen to examine, but also on the particular machinery present in particular cells or compartments within cells, for it is the latter that determines which parts of the signal remain intact and are contiguously read out and what the molecular results of the network of interactions involved turns out to be.<sup>10</sup>

As is generally known, there is cellular machinery that determines which stretches of DNA are accessible to RNA polymerases, where it is that the RNA polymerases get stopped or knocked off the DNA (both dependent, for a given stretch of DNA, on physiological conditions), and how the resulting RNA is processed – immediately in prokaryotes and before it can get through the nuclear membrane in eukaryotes. It is worth recalling at this point, that in eukaryotes, most genes are processed in such a way that the material corresponding to introns must be snipped out of the RNA molecule in order for the transcript to get through the nuclear membrane. At least occasionally, some of the material thus snipped out is, in turn, translated to yield a functional polypeptide (or is functional in some other way), so that it is natural to talk of one gene embedded inside another.<sup>11</sup> There may still be further post-transcriptional processing of mRNA,<sup>12</sup> and, at

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<sup>9</sup> This is also the reason for which the genetic code cannot be determined (or determined up to permutations) by an examination of the structure of DNA or mRNA molecules alone. In different cellular context (nucleus vs. mitochondria, some species of organisms vs. others), there are sometimes some regular differences in the transfer RNAs. Thus, in a few cases, the same codon in different contexts codes for a different amino acid, or for a stop signal instead of an amino acid.

<sup>10</sup> [Added 2003:] For some amplification concerning the points raised in this and the next paragraphs, see chap. 12 and (Keller 2000, 2003).

<sup>11</sup> A brief technical description of such a case is given by (Singer and Berg 1991, pp. 705-706) for introns in the mitochondria of yeast.

<sup>12</sup> Alternative splicing is just one of many relevant post-transcriptional phenomena that are relevant here. (Gilbert 2000 and Singer and Berg 1991, pp. 578 ff.) provide helpful accounts of alternative splicing and other technicalities discussed below. This phenomenon again demonstrates the impossibility of employing the intrinsic features of the DNA or RNA alone to

that, what precise polypeptide sequence the RNA yields is still a function of the tRNAs in the relevant cytoplasmic location. Further, post-translational processing of proteins is, at least in some cases, critical to whether or not the product that results in fact enters into a final product that plays a functional role. Complications of the sort involved in the rec-A and immune system cases go on and on in many more ways than can be discussed here.

Perhaps a quasi example will make the point clearer. Consider an ORF (that is a signal that opens a reading frame on a stretch of DNA), located by appropriate molecular techniques. Does the ORF mark the beginning of, or even delimit, a gene? The answer, so far as there is one, depends on the physiological context, the alternative splicing and readout controls present in the relevant cell (for the stop signals are different in mitochondria than in the nucleus), the tRNAs present in the immediate context and so on and on. Often enough, a single ORF begins a transcript that contains multiple genes.<sup>13</sup> My conclusion is that even when one works at the molecular level, what counts as a gene is thoroughly context dependent.

The arguments just presented interact constructively. Conceptually speaking, what counts as a gene depends on what one chooses as a phenotype. What one may choose as a phenotype, however, is somewhat constrained by what we learn about genes. Factually speaking, how one may delimit a gene at the molecular level depends on the entire system for processing DNA, RNA, the translation of processed RNA into protein, and also post-translational processing. As a result, the task of delimiting genes contains an inextricable mixture of conceptual and factual elements. To be sure, the ‘lowest’ level’, i.e., the molecular level, though it is most distant from naive observation, brings the argument closer to a context-fixed factual basis than the others. But the price for this is that one must deal with the interactions of all of the relevant macromolecules within their physiological setting. This has the consequence that precise definitions of genes must be abandoned, for there are simply too many kinds of genes, delimited in too many ways. Taken in combination, these arguments combine to provide powerful support for the principal contention of this chapter, namely that when we reach full molecular detail we are better off to abandon specific gene concepts and to adopt, instead, a molecular biology of the genetic material.

### Postscript 2003

Since 1995, much new attention has been given to the issues discussed in this chapter (e.g., Beurton, Falk and Rheinberger 2000, Dietrich 2000, Griffiths and Neumann-Held 1999, Kay 2000, Keller 2000, Morange 1996, 2000, 2001, Moss 2001, 2003, Neumann-Held 2001, Portin 2002, Sarkar 1998, Snyder and Gerstein 2003, Waters 2000). One line of work is of special interest for the position staked out above – to wit, attempts to provide intrinsically-molecular concepts of the gene. An important effort in this direction is Lenny Moss’s *What Genes Can’t Do* (Moss 2003). (For a contrasting approach to this problem see Waters 1992, 1994, 2000). Moss distinguishes sharply

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determine which stretches of a DNA or RNA molecule produce “biologically active RNA.” For further explanation of many of the issues discussed below, see chap. 12.

<sup>13</sup> Chapter 5 of (Gilbert 2000), which covers differential gene expression, includes useful reviews of differential RNA processing (pp. 130-133) and of (contextually variable) translational and post-translational controls of the end products of the expression of nucleotides sequences (pp. 134-136).

between two sorts of gene concepts, labeled *gene-P* and *gene-D*. Although the label *gene-P* is meant to capture the connection between preformationism and genes that somehow determine a phenotype, a gene-P is defined as a gene *for* a phenotype (i.e., one that is identified by its causal link to that phenotype) (see Moss 2003, p. 45). In contrast, a *gene-D* (the “D” indicates that the gene is interpreted as a developmental resource) is defined by its molecular sequence (i.e., intrinsically, without reference to what it produces). Moss rightly insists (as was argued above) that a nucleotide sequence may enter into many different interactions and may be processed so that the products it yields have many different structures and occur in many different tissues. Similar things may be said for non-coding nucleotide sequences and the reactions that they affect. Accordingly, it is simply incorrect to identify molecular sequences in terms of particular effects. No gene-D is properly understood as a gene for X, where X stands for a phenotype or a function; the effects of a gene-D depend on the biological context and (often) on the history of the organism. Hence, the effects of a gene-D are “*indeterminate* with respect to phenotype” (Moss 2003, p. 45).

This point about nucleotide sequences and the indirectness of their relationship to phenotypes is entirely correct. But I am skeptical of Moss’s deployment of the terminology of genes-D. The problem is how one delimits one gene-D from another. Not all nucleotide sequences should count as genes. Some short nucleotide sequences are repeated millions of times within the genome. Should each arbitrary length of such a sequence count as a distinct gene? For good reasons, even when one is working at the molecular level, it is often desirable to identify distinct nucleotide sequences as instances of the same gene – e.g., in numerous contexts in which the relation between a gene and amino acid sequences is at stake, synonymous substitutions are counted as alterations that do not change the identity of the gene, even at the molecular level. Moss would probably consider this a confusion of gene-P interpretations of the gene with gene-D interpretations of the gene. I consider it evidence that *even at the molecular level, functional criteria of delimitation are built into gene concepts*. The issues here obviously ramify far beyond this immediate, partly linguistic, partly conceptual point. Moss’s insistence that we take seriously the idea of a sequence-defined or sequence-delimited concept of the gene is salutary. The issue between us (if it turns out not to be a confusion on my part) is over the need to restrict sequence-based definitions with further (functional) criteria in order to save the gene concept from picking out any and all arbitrary sequences. If I am right, either way (and Moss may concur with this claim), the result is that, *the context-dependence of the effects of nucleotide sequences entails that what a sequence-defined gene does cannot be understood except by placing it in the context of the higher order organization of the particular organisms in which it is located and in the particular environments in which those organisms live*. This argument provides a synopsis of the one strand of support for the claim that the science of genetics has argued itself out of the most stringent versions of reductionism.

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