What is a gene?

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The biological study of heredity is relatively young in comparison to some endeavours in science, but it has matured quickly. Although, as Rheinberger and Muller-Wille point out, "It was only in the nineteenth century that heredity became a major problem to be dealt with in biology" (2009), it has risen in profile to become a central enterprise in the biological sciences: vast resources have been put towards sequencing the human genome, genetic screening/manipulation of offspring is a highly controversial possibility, and the DNA paternity test is a reality TV staple.

It might be expected that the effect of this maturation on the subject's central term, the gene, would be to clarify its meaning and increase the precision of its reference, leading to widespread agreement as to what a gene is. For example, such a process seems apparent in the development of the term 'atom' in physics: from its ancient etymology as a vaguely-defined 'indivisible thing', through the plum-pudding model and Rutherford scattering to the modern quantum mechanical picture, the advancement of physics has led to a gradually more detailed understanding of the constitution and interactions of the atom, and thereby to a stable consensus as to the term's meaning.

For the gene, however, this is emphatically not the case. Instead, the term remains "open to conflicting interpretations of its meaning" (Falk, 1986: 133), genetic research having produced a "proliferation of a variety of gene concepts, which sometimes complement, sometimes contradict each other" (Rheinberger, 2009). In this essay I will explore how this has become the case, and what attempts have been made to resolve it.

Proceeding from the comparison between the gene and the atom, an important initial difference between the two becomes clear. Physics is concerned with discovering and studying the atom as a physical entity. Even acknowledging the disagreement over the extent to which such entities are supposed to be fundamentally, metaphysically 'real', it is clear that the role of the atom as a constituent of matter requires it to be conceived of, within physical theory, as something that has physical existence; can be seen through a microscope, accelerated through a tunnel, and so on.

In contrast, the classical gene emerged from Mendel's idea of the "unit-character", inferred from observations of trait inheritance in plants and with no postulated physical constitution; it has even been characterised as simply "a practical device for aiding plant breeders" (Moss, 2008: 39). Falk describes this in terms of 'intervening variables' (1986: 134).

An intervening variable is "a quantity obtained by a specified manipulation of the values of empirical variables", (*Ibid.*) about whose existence or physical nature no claims are made. A simple example is a negative quantity of money: we might subtract the number of coins in one jar from the number in another and get a negative number which can be usefully put to work, but at the point at which we use our calculations to say something about the physical world, we should never end up predicting the existence of a negative number of coins.

The gene, as used by Mendel, is also an intervening variable – a theoretical abstract arrived at by synthesising empirical observations such as flower colour or leaf size, manipulated in theory-space, and then used to predict future empirical observations. In Mendelian genetics, it seems that it is just not part of the gene's portfolio of responsibilities for it to have a particular shape, size or indeed any tangible physicality at all.

If this were the full story of the classical gene, one might wonder how it could make sense to argue about the 'meaning' or 'nature' of a completely abstract theoretical term. However, despite the desire of Johannsen and others to "establish the 'gene' as … a pure 'intervening variable'" (*Ibid.*), such insulation of the concept from physical reality was not possible.

Stotz and Griffiths note that, as well as being intervening variables, classical genes were also "hypothetical material constituents of the cell whose physical transmission from parent to offspring causally explained the Mendelian pattern of inheritance." (2007: 86) That is, although Mendel's belief that the traits he observed were "related … to certain 'elements' or 'factors' in the reproductive cells" (Rheinberger, 2009) committed him to very little beyond the basic notion that *something* is responsible for transmitting traits between generations, even that small commitment imposed the requirement that there be some existent, worldly entity or entities doing the causal work required of the gene. Once this is granted, the question of their physical nature is difficult to ignore. As Mendel's experiments show, it is perfectly possible to in some sense 'do genetics' (insofar as making predictions and

explanations involving the gene) without being concerned about its physical basis. However, the gene's role as a causer of observable effects requires it to have *some* physical basis, the study thereof being interesting and inevitable, particularly given the tendency of the physical and chemical sciences to examine nature at progressively smaller scales. The resulting attempts to give the gene firm physical status have been responsible for much of the conceptual diversity surrounding it.

The advent of serious enquiry into the gene as a physical entity can be framed (Griffiths, 2007) in terms of the departure from Thomas Hunt Morgan's school of classical genetics of his student, Herman Muller. Morgan held the view that "at the level at which genetic experiments lie, it does not make the slightest difference whether the gene is a hypothetical unit, or whether the gene is a material particle" (*Ibid*: 87). This willingness to consciously ignore the question of the physical nature of the gene was not shared by Muller, who began his own programme predicated upon a conception of the gene as a "molecule-like" entity (Falk, 1986: 152).

The new science engendered by this outlook is well illustrated by the experiments of Timofeéff-Ressovsky, Zimmer and Delbrück, who made estimates of the 'size' of the gene from the amount of radiation required to cause mutation (*Ibid.*). The fact that these experiments could be imagined indicates the changing scientific attitude towards the gene, since without the basic premise that the gene is physical, molecular, somehow 'like' an enzyme or bacteria (which had also been investigated using radiation), attempting to measure its size in such a way would hardly make sense.

Stotz and Griffiths characterise Muller's work as an effort to find an "epistemic pathway to the gene that bypassed the observed effect of the gene on the phenotype" (2007: 89), and this talk of epistemic pathways is in my view extremely useful in comparing the two approaches to the gene. The pathway used by Mendel and Morgan involves inferring knowledge about what is considered an unobservable entity from that entity's observable effects, and works with an instrumentalist concept of the gene. Although, as I have argued, this approach suggests the presence of *some* physical thing underwriting the causal efficacy of the abstract gene, it does not attempt to say anything about its physical nature. Therefore, we could continue indefinitely along this pathway without gaining any real understanding of what a gene physically is.

The molecular-genetic programme, in which the physical features of the (now) physical gene become a primary subject of enquiry, cannot, therefore, be characterised as a simple furthering of the pre-existing, classical-genetic programme. Molecular genetics was "not a direct follow-up of classical genetics," but instead came about as part of an "overall molecularization of biology driven by the application of newly developed physical and chemical methods" (Rheinberger, 2009). That is, the molecular programme represented not a direct continuation of previous work but a new way of attacking the problem, based upon the idea that new scientific methods could open avenues of enquiry that did not rely solely on inferences from the gene's observable effects on the phenotype.

Broadly speaking, we have a picture of two co-existing epistemic pathways to the gene, constituting two very different notions of how the gene should be conceived of, and to what methods of investigation it might be amenable. Despite this, Falk is keen to recognise a "constant mutual interchange" (1986: 152) between the two. For instance, Muller's investigations into radiation-induced mutation made use of the knowledge that, like the instrumentalist gene, the physical gene should be mutable ("in order to create heritable variation") (Griffiths 2007: 89). So, although the two pathways are distinct, they are not independent. In particular, the instrumentalist gene confers on any potential physical representative certain required functional properties such as mutability and self-replication (*Ibid*.). Thus, the molecular-genetic pathway did not simply abandon the classical gene for a new direction – instead, it sought a different route by which to eventually arrive at the same (as yet, unknown) destination. In the mid-twentieth century, deoxyribonucleic acid appeared to be that destination.

El-Hani (2007: 298) credits Watson and Crick's proposal of the double-helix model of DNA with allowing the physical gene to "triumph over the instrumentalist view" but, given the above recognition of the interdependence of these concepts, that seems quite an unfair (not to say dramatic) description. Rather, his account of the molecular gene's being defined as "a stretch of DNA that encodes a functional product, a single polypeptide chain or RNA molecule," thereby, in one concept "bringing together the structural and functional definitions of a gene" (*Ibid.*) suggests a coming-together of the two concepts, the molecular-genetic programme finally succeeding in providing a candidate both physically well-defined, and able to fill the functional roles which the classical-genetic programme had established for it. This

system of DNA, RNA and proteins, and the associated mechanisms by which the code is duplicated and gives rise to the phenotype, "turned out to be nearly universal for all classes of living beings" (Rheinberger, 2009). For a short time, biology seemed to have arrived at the hoped-for situation in which "[t]he functional definition of the gene that underlay genetic analysis and the structural definition of the material gene had turned out to be two ways to pick out the very same thing" (Griffiths 2007: 96). This did not last. In the advancement and increasing complexity of molecular genetics, the "coherent relationship between genes at the molecular level and Mendelian entities [instrumental genes]… would not survive the increasing understanding of the architectural diversity of the molecular gene" (El-Hani, 2007: 299).

El-Hani's above use of the word "Mendelian" in the context of DNA-based genetics brings to mind a strange but instructive scenario in which we try to imagine a resurrected Mendel mapping the results of his experiments onto the molecular-genetic picture of the 1950s.

The phenotypic traits that Mendel dealt with were, naturally enough, traits recognisable on a macroscopic level to an average human being: flower colour, roughness of leaf and so on. In Mendelian genetics, 'genes' for these traits would be postulated and used to explain and predict inheritance patterns – a gene for blue flowers, perhaps, or a gene for a particular leaf shape. How would Mendel proceed if asked to frame these genes in terms of discrete stretches of DNA?

Perhaps there is a stretch of DNA whose sole function is to produce blue flowers, which can be replaced with a slightly different stretch that instead produces red flowers. But then, what about purple flowers? Are these somehow the product of a combination of the two other genes, or of another separate gene? And if the blue-flower gene were removed without being replaced with any other, would we expect simply to grow a plant with no flowers, or would it fail to germinate at all?

Recognising the different scientific environments that Mendel and molecular geneticists inhabit, we might attempt to dismiss these questions by saying that because the traits Mendel worked with were arbitrary, chosen to be conveniently classifiable and easily recognisable, without consideration of the molecular structure of the gene, there is no reason why coarse-grained, anthropocentric features like colour or texture should correspond on a one-to-one basis with sequences of DNA.

Rather, we might argue that these macroscopic features should be recognised as the product of lower level features, continuing until we reach a level comparable in scale to DNA itself, at which we can say that the term 'gene for such-and-such a feature [now, RNA or polypeptide chains]' refers unambiguously to a particular DNA segment.

But even at this scale, there exist complexities which make the picture of single segments of DNA corresponding neatly to single proteins seem hopelessly optimistic. For example, in the snail *Aplysia*, one segment of DNA produces 11 separate protein products, and conversely, "the genomes of most higher organisms appear to comprise huge DNA stretches to which no function can as yet be assigned" (Rheinberger, 2009). These, and many more such examples, are discussed at length elsewhere (*Ibid.*), the sum total being the realisation that "[t]he relationship between structural [i.e. physical] genes and gene-like functions is not one-to-one but many-to-many" (Griffiths 2007: 98). No matter how far genetic research has progressed, the scenario whereby a discrete physical entitiy is unambiguously identified as the 'gene for' a particular functional product (be it a Mendelian macro-feature or a microscopic protein chain) has failed to materialise.

We have seen so far that attempts to bring together the instrumental and physical gene, despite appearing on the verge of success with the discovery of DNA, have subsequently been thwarted by unforeseen complexity in molecular-genetic processes.

Given this, Moss has tried to re-separate the two concepts in the face of what he identifies as the popularised view of the gene as a "master-molecule, or blueprint, that is specified simultaneously by its nucleic-acid sequence and its phenotypic consequence" (2008: 45). He does this by providing two distinct terms: "Gene-P" and "Gene-D". His Gene-P is something that has a "predictable relationship to the appearance of a certain phenotype", in the vein of the original Mendelian gene, with the added proviso that the term is "indeterminate with respect to DNA structure" (*Ibid.*). The explicit inclusion of the Morganian requirement that, in situations where Gene-P is deployed, its physical composition and nature should be ignored to the point of exclusion, protects against the creeping physicalisation of an abstract entity, which had led Muller to begin the hunt for a molecular gene in the first place. In place of the molecular gene comes Gene-D, which is "defined by a molecular, i.e., DNA,

sequence but is indeterminate with respect to phenotype" (*Ibid.*: 42). Together, the two terms are intended to cover all the referential ground that the gene does, while making clear that its meaning consists of two distinct components which must not be conflated.

Moss provides a compelling argument in support of Gene-P, by making the point that in the majority of cases where a phenotypic trait is identified, it is found to correlate not with the presence of a specific DNA sequence, "but rather the absence of some 'normal' sequence resource" (*Ibid.*)., and therefore has the potential to be identified with many distinct DNA sequences lacking that resource. The particular example he gives is of "over 900 different documented DNA sequences that may show up as 'the gene for cystic fibrosis'" (*Ibid.*). In this kind of situation, talk of the 'gene for cystic fibrosis' refers to a very different entity (or lack thereof) than the kind of gene that might exist as a particular stretch of DNA and be viewed or manipulated under a microscope, potentially giving the general public the impression (until recently, shared by the author) that once identified it could be simply and easily screened for – in fact, as Moss points out, a different genetic probe is in principle required for each of the myriad ways in which the abstract 'cystic fibrosis gene' can be physically instantiated (*Ibid.*). The potential of the P/D distinction to prevent such biomedical misunderstandings is attractive – indeed it would seem strange to argue that a conflation of the type described above could possibly be desirable in science.

An interesting response to the Gene-D side of Moss's distinction is made by Richard Burian. For him, "[t]he problem is how one delimits one Gene-D from another," (2005: 176) that is, how should these entities, which are defined purely by their structural form, be a) identified, and b) distinguished from one another? He notes, for instance, that some arbitrarily small sequences of DNA "are repeated millions of times within the genome" (*Ibid.*) and hence questions whether any satisfactory identification and delimitation of genes, even at the molecular level, can be achieved without recourse to "functional [i.e. *not purely structural*] criteria of delimitation" (*Ibid.*). This discussion raises the possibility that the concept of a gene 'purely-D' might not be coherent, suggesting that the only difference between the instrumental and molecular gene is the scale at which the functions by which we define it take place – its 'scale of functionality'. If this is the case, it may turn out that there exists not a dichotomy of the two gene concepts P and D, but a hierarchy of Gene-P-like concepts, each defined in relation to its own scale of functionality.

The concept of the gene has mutated and multiplied since its inception, its initially vague, pragmatic definition giving rise to the competing concepts of the instrumental and physical gene. With the rise of molecular biology, both concepts appeared to have converged on a stable physical reference point, DNA. However, as increasing complexity at the molecular level emerged, it became apparent that the two gene concepts could not be brought together without severe and potentially troublesome conflation of meaning. I have elucidated Lenny Moss's attempt to pry the concepts apart and argued that, while his Gene-P constitutes a valuable reminder of the functionally-defined way in which the term 'gene' is commonly used (particularly in medicine), the notion of an entirely structurally defined Gene-D may not be coherent, raising the possibility that what a gene is physically identified with may depend in large part upon the scale of functionality at which it is being used.

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