Causal selection in context: explaining gene centrism

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Draft last updated 12 June 2023

Abstract

There are two problems in the history and philosophy of genetics that seem to be related, but it is not yet clear just what that relationship is. One is the problem of causal selection, and the other is justifying gene centrism – the general approach of seeking genetic explanations. I argue that to understand the relationship between the two, we must consider explanatory targets far causally downstream from DNA. Philosophers have identified causal specificity as an intrinsic feature of genetic causes that makes them explanatorily relevant for very close downstream targets in the cellular environment of DNA. But when explaining targets far downstream, biologists sometimes select as explanatory causes that are genetic but not specific, and other times select causes that are specific but not genetic. This observation detaches causal specificity from causal selection, and in turn, from gene centrism. I argue further that specificity cannot justify gene centrism in virtue of its contribution to the utility of genes as tools. I propose instead that the persistence and scope of genetics is better explained by a variety of historical factors. My analysis illuminates two conclusions: first, the success of genetics is what explains the prevalence of specificity as a criterion of causal selection, and not *vice versa* as philosophers have previously argued. And second, the objective and pragmatic dimensions of causal selection are interdependent.

Introduction

Biologists and philosophers agree that the complex interaction of genes and many other factors is responsible for the growth and development of organisms. Even though we have arrived at this interactionist consensus that genes and environment both *matter*, we have much more to explain. The interactionist consensus leaves plenty of room for important differences among the many causal factors in development, and these differences are worth investigating. Further, genetics has been a hugely influential and productive research program, whereas environmental

factors have, on the whole, received less attention and play less of an organizing role in the study of development. The methods of genetics have coalesced into a general program sometimes called 'gene centrism.' C. Kenneth Waters describes gene centrism as a methods-driven research program organized around the extension and development of genetic technology, rather than a central theory (Waters 2006).

It is reasonable, then, to think that there might be something that distinguishes genetic causes from the others, and therefore that there is an important relationship between the causal character of genes and the popularity of the genetic research program. If there is something special about genes or their role in development that sets them apart from other factors, that special feature could constitute a criterion for causal selection – the process of picking out one or more causes of a target phenomenon as the *explanatory* cause(s). In turn, this could form an "objective" justification for the success of the genetic research program. I will argue that special properties purported to underlie the selection of genetic causes as explanatory– in particular, the popular concept of *specificity* – do relatively little to account for the success and persistence of genetics. And, perhaps more interestingly, there is an important relationship in the opposite direction: the success and persistence of genetics helps to explain why we have identified specificity as such an important criterion for causal selection.

Philosophers typically study causal selection by examining the successful explanations of scientists. They resist the idea that scientists prefer to cite certain causes over others for capricious or unprincipled reasons, and they look for features of causes that make them valuable for our existing standards of explanation. One such feature is *fine-grained causal specificity*. A maximally specific cause is one which takes several values, and for each distinct value of the cause, setting the cause to this value produces one or close to one distinct outcome (Waters 2007).[1] Philosophers then typically extrapolate – finding causes with specificity in successful explanations supposedly shows us that specificity is an intrinsically important causal property. I will argue that what it actually shows is more historical. The success of genetics is fueled by many epistemic, technological, and sociological factors. It is these factors that produce the sample of successful biological explanations, from which specificity is then extracted as the criterion for causal selection.

[1] Though there are other notions of specificity, it is fine-grained specificity that I am concerned with in this paper, and all further mentions of 'specificity' refer to fine-grained specificity.

Most discussion on causal specificity has been focused on the intracellular environment surrounding DNA – often the process of protein synthesis. But if we examine explanatory targets further downstream, like the traits of developed organisms (the phenomena that drew scientists to genetic explanation in the first place), specificity seems to be a much weaker factor in accounting for gene centrism. As we will see, our focus on specificity biases the sample of successful explanations for analysis of causal selection.

I structure the paper as follows: In Section 1, I show how specificity is related to gene centrism via the problem of causal selection. In Section 2, I argue that to understand the relationship between gene centrism and causal specificity, we need to 'zoom out' to explanatory targets that are much more causally downstream from the DNA sequence – developed traits of organisms. I show several examples that help to detach specificity from causal selection among genetic and non-genetic causes in successful explanations. I conclude that specificity, via causal selection, cannot do much to account for gene centrism. In Section 3, I consider the possibility that specificity might underlie the utility of genes as tools and argue that it does not. This helps to illuminate two conclusions. First, the success of genetics as a research program is what explains the prevalence of specificity as a criterion of causal selection. And second, the objective and pragmatic components of causal selection are interdependent – the features we should use to pick out the explanatory causes of a phenomenon do not follow neatly and separately from our explanatory aims.

1. Connecting Causal Selection to Gene Centrism

There are two connections between causal selection and gene centrism. On the one hand, philosophers have taken successful biological explanations as a sample to search for causal selection criteria for scientific explanation in general. On the other, philosophers have taken the properties identified by those criteria to constitute an important distinction between genes and non-genetic causes – thus helping to justify gene centrism.

The general philosophical problem of causal selection arises in any account of causal explanation. In particular, on a minimal interventionist account like that of Woodward (2003), no effect truly has a single cause. If causes explain their effects, it should follow that each cause features equally and necessarily in the explanation of

the effect of interest. However, scientists and non-scientists alike routinely cite only one or a subset of causes as explanatory, leaving the rest aside as irrelevant to explanation. A lit cigarette dropping to the ground and the presence of surrounding oxygen would both count as causes of a fire (Hart and Honoré 1959). But intuitively, the dropping of the cigarette, not the presence of oxygen, explains the presence of the fire. This case is typically resolved by appealing to some notion of structuring versus triggering cause – the oxygen is, in an important sense, in the background (c.f., Mackie 1974; Dretske 1988; 2004). But is there a principle that can be systematically applied across contexts to determine which causes are explanatory and which should be backgrounded?

Biological systems are extraordinarily causally complex, so they provide many examples of successful explanations despite vast causal complexity. This makes them, in Laura Franklin-Hall's words, "a gold mine for those wanting to identify the selective patterns to which a philosophical account [of causal selection] is responsible" (Franklin-Hall 2015). In her view, searching successful explanations is the best way to identify causal selection criteria, and biological explanations in particular form a good sample.

When philosophers identify these criteria for causal selection, they typically hope that it is based on some intrinsic (sometimes "ontological") feature of the cause, rather than mere preference – or at least, there is some principled reason for choosing one cause over the other. It is traditionally held that causal selection must be pragmatic (Mill 1884; Mackie 1974). Causal selection must, of course, have something to do with our explanatory aims, and thus must always be pragmatic in some sense. But if scientists prefer one cause over another for the purposes of explanation simply because they have an arbitrary or unjustified preference for one, causal selection is not only pragmatic but *capricious*. Lauren Ross has pointed out, however, there is slippage in the literature between the inevitable pragmatic nature of causal selection and the more problematic accusation that causal selection is capricious (Ross 2019). Ross has proposed that causal selection within a particular domain is supported by a context-dependent *rationale* that incorporates "objective" reasons and also depends upon the interests of the investigators. This dual-featured account of causal selection – explanatory aims on one side and objective causal features on the other – gives us a *principled* account of causal selection.

We can begin to see that this is relevant to the connection between gene centrism

and causal selection. It could be that some intrinsic property of genes, namely specificity, supplies the objective component to causal explanation. This would mean that if scientists prefer genetic explanations, they do not do so arbitrarily. If causal selection of genes is *capricious*, though, then we should hardly expect its capricious underpinnings to justify gene centrism. To be clear, no one expects that genes have a magic property that excludes or fully eclipses any other reasons for the success and persistence of genetic research. But it is in the first place a reasonable question to ask whether there is *some* relationship there, and indeed those authors who have investigated specificity as a property typically draw some implications in this direction. A prominent example is C. Kenneth Waters (2007). His work addresses both the Developmental Systems Theory (DST) thesis of *parity* among causes of development, and the general question in causal explanation regarding causal selection. Though there are several ways that philosophers have stated and interpreted the DST parity thesis, Waters interprets causal parity as what Ulrich Stegmann calls "Millean parity" – whatever empirical differences we might find between the role of genes in development and the role of other factors, the factors belong to the same ontological category of *causes* (Stegmann 2012). Waters responds to the idea that there is no intrinsic feature of the cause that we can point to in order to distinguish genetic causes from the others, and he suggests that the answer "reveals important clues for understanding why so much research attention in developmental biology is centered on DNA" (Waters 2007, 21).

Waters argues that there are in fact intrinsic differences among causes – actual difference making and causal specificity – and, in particular, genes are the specific actual-difference makers in development. (Waters 2007). Actual difference making can be summarized as follows: in a given population and with respect to a fixed explanatory target, many causal variables may be identified counterfactually, but only some of those causal variables take on different values among the members of that population. Others take the same value in each member of the population. DNA sequence, he argues, is an actual difference maker with respect to RNA sequence in the process of protein synthesis. In contrast, the enzyme RNA polymerase is only a potential difference maker with respect to RNA sequence. It is always present in the cellular environment, so even though an intervention to vary its presence or character *would* affect the RNA sequence, no such variation exists in typical cells.

Further, he argues that actual difference making, together with causal specificity, underlies the selection of genetic causes in explanations of growth and development.

The fact that genes alone among causes possess *both* these features, he argues, helps to explain why genes are selected as explanatory and why biologists are so focused on genes more generally.

When there are multiple actual difference makers, as there are in protein synthesis in eukaryotic cells, Waters contends that DNA has the further special property of fine-grained causal specificity. Waters articulates this notion of causal specificity by combining features from Lewis' account of causal influence and Woodward's account of interventionist causation: in a causal relationship where X causes Y, a X has fine-grained specificity if it takes many finely incremented values, and these values produce correspondingly fine difference in value of Y (Lewis 2000; Woodward 2003). DNA is a specific difference maker because "changes in the sequence of nucleotides in DNA would change the linear sequence in RNA molecules in many different and very specific ways" (Waters 2007, 23).

Given our explanatory aims, the specific actual-difference makers are the causes that scientists cite as explanatory, and because that decision is based on a property of the causes and not simply a preference for one of several equivalent members of the ontological category, we can say that causal selection of genetic causes is justified. For Waters, causal selection in general is principled, and in particular, it is principled in the case of genes as causes of growth and development. Further, the same features that make those causal selection decisions principled help to explain why there is so much focus on genetic causes in biology. There really is something 'special' about genes that makes them suited to our more general and independently justified aims of science. His picture is explicable in Ross's framework: there is an objective side to the selection of genetic causes (actual difference making and specificity), set by our preexisting explanatory aims. Waters then suggests that understanding how specificity makes genes explanatorily relevant causes also helps us understand why there has been such a strong focus on investigating genetic causes for traits (Waters 2007, 21).

In contrast to Waters, Lisa Gannett argues that causal selection *and* gene centrism are capricious – biologists have an arbitrary preference for genetic investigation and explanation (Gannett 1999). She gives this argument mainly as a criticism for what she sees as a largely unchecked geneticization of disease. In this strong version of an argument against principled causal selection, Gannett criticizes the discipline of genetics by arguing that biological researchers falsely believe that genes are more

tractable than their non-genetic or environmental counterparts, especially with respect to producing disease phenotypes. She suggests that they do so for unprincipled reasons; environmental factors have "perceived unwieldiness" and the belief in the tractability of genes stems from an avoidance of complex problems (Gannett 1999, 370). The reasons for singling out genes as particularly explanatory has to do with the extra-scientific goals and preferences of the scientists involved, rather than any intrinsic feature of genes as causes. On Gannett's view, there is no 'objective' criterion for causal selection for biologists to systematically apply out once they have specified their explanatory target.

In general, philosophers of biology have resisted strong claims of capriciousness like Gannet's. Waters' view that specificity is a significant property of genes is taken as the received view among philosophers (Planer 2015; P. Griffiths and Stotz 2013; Neal 2019; Weber 2017b). Further, specificity has become a very important concept in the philosophy of causation, quite apart from its relevance to genetics (P. E. Griffiths et al. 2015). So while no one believes that specificity alone explains every case of causal selection or every aspect of gene centrism, the connection between the two is both present in the literature and *prima facie* reasonable, and as such is worth investigating. Does specificity provide the objective dimension of causal selection in explanation of growth and development, and does that justification carry through to account for gene centrism? In the sections that follow, I will show that it does not. Instead, the historical development of gene centrism helps to explain why specificity is identified as important for causal selection, and thus there is an important interdependence between the objective and pragmatic dimensions of causal selection. These insights qualify the generalizations about causal selection that we can make from successful biological explanations, but they need not lead us to an extreme view like Gannett's.

2. Specificity: The Objective Dimension of Causal Selection?

Much of the discussion on specificity of genetic causes is localized to the intracellular environment, especially the immediate molecular environment of DNA. Waters constructs his causal selection account from an example of RNA molecules with a particular nucleotide sequence produced using the DNA template. This explanatory target is closely causally downstream because there are relatively few causal steps (in this case, molecular processes) between the cause (DNA sequence) and the effect of interest (RNA sequence). There are many more steps between DNA sequence and a

developed trait, e.g., an organism's adult size, than there are between DNA and RNA sequence.

Paul Griffiths and Karola Stotz argue that even 'zooming out' slightly, to cellular processes beyond protein synthesis, presents problems for the causal specificity of DNA sequence (P. Griffiths and Stotz 2013). Others have made similar claims about gene regulatory networks (DiFrisco and Jaeger 2020). Here, I will fully 'zoom out,' to the level of the trait in a developed organism, which is the level of the original targets of the study of heredity (as even some biologists have recently pointed out, e.g., Orgogozo, Morizot, and Martin 2015). Traits are also the focus of the paradigmatic works of DST, which are some of Waters's primary targets (e.g., Oyama et al. 2001; Oyama 1998; P. E. Griffiths and Gray 1994).

Rather than, e.g., the sequence of RNA molecules or even the identity of protein products of genes, developed traits include things like eye color or adult body size. It is worth considering these downstream explanatory targets because gene centrism, of course, encompasses much more than the immediate cellular environment of DNA molecules.[2] It is for these explanatory targets that specificity does not serve as a reliable criterion for causal selection, and therefore does not to help much in accounting for gene centrism. One might worry that this is not a relevant objection – Janella Baxter argues that objecting to the scope of actual difference making and specificity is just to miss Waters' larger point, which is that actual difference making is a solution to causal selection (Baxter 2021). The fact that this property is not unique to DNA sequence, she argues, does not threaten actual difference making as a refutation of the causal parity thesis. But it is important here that Baxter, following Waters, is interpreting the DST parity thesis as Millean parity and therefore identifying the parity thesis with the general philosophical problem of causal selection. But recall that Waters makes clear that his aim is not only to introduce a property we might use to distinguish among causes, but also to explain why "so much research attention is centered on DNA" (Waters 2007, 21). If Waters' only aim were to refute the Millean causal parity thesis, actual difference making might have been enough – but it is not enough to justify gene centrism. Actual difference making and specificity are neither unique to DNA nor a ubiquitous property of

[2] Waters, more recently, points out that genetic explanations that rely on specificity are extremely limited to the "temporally" and "biologically" close effects within the cell though he uses a concept of *temporal* proximity to DNA sequence. (Waters 2019).

selected causes in growth and development, both genetic and non-genetic. The extent to which specificity accounts for gene centrism *does* depend on how often DNA actually exhibits specificity in successful explanations. To show this, I'll introduce several examples that detach causal specificity from causal selection in the context of biological growth and development.

2.1 Some Selected Causes are Specific but not Genetic

Consider the phenomenon of developmental phenotypic plasticity. This is the ability to develop different traits in response to an environmental stimulus. Recent work has uncovered phenotypic traits with dosage-dependent responses to environmental factors. In these cases, incremental changes in the value of a non-genetic cause result in similarly incremental changes in the value of the phenotypic trait, meaning that such non-genetic causes have fine-grained specificity.

Ecologists Nancy Schoeppner and Rick Relyea have shown evidence that fine incremental increases in the density of predators in an organism's environment causes size differences in prey that are also finely incremented (Schoeppner and Relyea 2008; 2009). This means that predator density is a specific cause in the same sense that Waters describes for DNA sequence causing RNA sequence. Schoeppner and Relyea use a model organism, larval anuran (wood frog tadpoles, species *Rana sylvatica*). The tadpoles were exposed to an "increasing gradient of predation risk," in order to "determine how organisms respond to small environmental changes." Predator presence was manipulated in two ways: "by altering the amount of prey consumed by a constant number of predators (*Dysticus sp.*) and by altering the number of predators that consume a constant amount of prey." They found that traits, e.g., various measures of body size, all exhibited a fine-grained response to incremental increases in predator density.

On an interventionist account of causation, predator density is clearly a cause of body size, because interventions on predator density reliably produce changes in body size. Among populations in different local environments in which predator density actually differs, body size differs, and so predator density is an actual difference making cause. Predator density is also a *specific* actual difference making cause: it is the fine-grained increases in predator density that produce fine-grained, graded responses in body size. From this example, we can see that biologists select causes which are specific, though non-genetic. This is one limitation on the role of

causal specificity in justifying gene centrism. Developmentally plastic traits like body size are sometimes explained by a specific, though non-genetic, actual-difference maker.[3]

2.2 Some Selected Causes are Genetic but not Specific

Often when a gene appears to be the only actual difference making cause of a trait, it is not causally specific for its target. There are further cases in which a gene is not specific, yet it is selected over other, non-genetic, specific, actual difference making causes. In the former category, several paradigmatic genetic diseases are said to be explained by a genetic causal factor, where the mutated gene is the only actual difference making cause. One prominent example is Huntington's Disease, which is caused by mutation in the HTT gene. Huntington's Disease, along with others like Tay-Sachs's Disease and sickle-cell anemia are common even in biology textbooks as exemplars of genetic disease. But in such cases the genetic cause is not specific in Waters' sense. The presence or absence of the mutation is binary, and the disease phenotype is also binary, so it is not the case that many fine-grained changes to the causal variable produce correspondingly many fine-grained differences in the effect. However, these are decidedly genetic diseases – their phenotype is explained by the genetic mutation that causes them.

More powerful are examples in the second category – in which genes are among several actual difference making causes, they are not specific, and they are still the primarily selected cause. I will use the example of Phenylketonuria (PKU) here for its familiarity, but in fact the phenotype of *any* genetic disorder involving the inability to process some metabolic substance will have at least a mutated allele and a metabolite as actual difference making causes (Galactosemia is another example). PKU is characterized by an inability to break down the amino acid phenylalanine when it is consumed in the diet. The disease phenotype includes severe cognitive impairment, organ damage, unusual posture and severely compromised pregnancy (Cederbaum 2002). It is caused by a mutated allele in the PAH gene that prevents the body from producing enzymes needed in order to break down those substances.

[3] It may be that the response in body size is achieved through a gene regulatory pathway. However, this does not mean that predator density is not on its own a specific cause. Moreover, maintaining *proportionality* in this causal explanation (Woodward 2010) favors selecting predator density over the mediating gene regulatory pathways.

The disease phenotype that biologists define and seek to explain is the effect of the reduced or absent processing of the metabolite. Because the severity of the disease phenotype depends on the amount of the metabolic substance, the consumption of that substance is a specific, actual difference making cause. Different mutations in the PAH gene can contribute to the severity of the PKU disease phenotype, but the relationship appears heterogenous and not specific: "…the notion of genotype-phenotype correlation [in PKU] has been shown to be relatively unhelpful or relatively incomplete, and…substantial genetic heterogeneity is known" (Cederbaum 2002, 702). Much *more* variation in disease severity is explained by consumption of phenylalanine. Indeed, PKU is primarily treated with a restricted diet in which one does not consume phenylalanine. The level of phenylalanine consumption is, then, a specific, actual difference making cause. Moreover, phenylalanine consumption is a more specific cause than are the mutated alleles. In this case, the genetic cause is selected over another specific, actual difference making cause.

These examples are helpful in showing in detail that non-genetic causal factors and non-specific causal factors are in fact cited by biologists as explanatory. Such examples are not idiosyncratic to explanations of disease phenotype. Janella Baxter argues that gene *expression* levels, in contrast to gene sequence, control phenotypes with fine-grained specificity and are *often* the relevant feature for causal selection in explanations of developmental biology (Baxter 2021). This is a significant contrast to specificity of the DNA sequence. Taken together, these cases help to complete the separation of specificity from genetic causes and from selected causes for downstream explanatory targets.

3. The scope of gene centrism and the supply of successful explanations

We saw in the previous section that, even if specificity is sometimes the basis for causal selection, it does not reliably pick out genes as the (or an) explanatory cause across scales of gene action, and so it does not go very far in justifying gene centrism. But there is, at this point, a natural response to consider. While there is no strong connection between specificity as a criterion for causal selection gene centrism, perhaps we should look outside the context of causal selection. Perhaps causal selection is too focused on explanation, as gene centrism is a broad research program, not a strict explanatory framework. Waters also argues that that biologists focus on genes because genes are uniquely *useful* in biological practice, and that genetics progresses by extension of its techniques, rather than by fleshing out a

central organizing theory (Waters 2004; 2019).

But what makes genes useful? Is it a causal property like specificity? Perhaps specificity underlies causal selection for explanatory targets in the proximate molecular environment of DNA, and then, because genetics was so successful there, its explanatory scope expanded outward, to include targets further and further downstream. If so, specificity would directly explain the success of genetic approaches to the molecular environment of cells, and indirectly explain the breadth of the explanatory scope of genetics. It would also mean that selection of genetic causes follows from the more general utility of specificity. There are at least three problems with this approach.

First, the molecular genetic tools developed for the manipulation of causal relationships proximate to DNA sequence sometimes exploit specificity, though not always. They do typically exploit sequence specificity with respect to complementary DNA or RNA strands. But they do not always exploit *specificity with respect to RNA product*, and certainly not to more downstream targets. Recall Baxter's example above – gene knockout and gene knockdown experiments both exploit the DNA sequence associated with a product expression level, but not necessarily the specificity of the DNA sequence with respect to the RNA product identity.

Second, while there is no denying that specificity of gene sequence with respect to pre-mRNA sequence has proved useful, this is not enough. Like any tool, genes are not useful solely because of their properties, but because we have the means to take advantage of those properties. Even if specificity is useful, it cannot on its own explain why genes are useful tools in contrast to other factors. Because of the limitations on the scope of specificity's role in causal selection, specificity cannot explain *why* so many explanatory targets – even those which is likely *not* controlled by specific modulation of DNA sequence – seem to fall within the purview of gene-centric research.

Genetics began as the study of inheritance, especially with respect to human traits – it cannot be the case that specificity drives the extension of gene centrism by the application of techniques, because those targets were within gene centrism from the start. In the Morgan school's study of inheritance, downstream explanatory targets were already considered within the purview of genetics. This was because they were the explanatory targets of the study of heredity in general; studying the underlying

processes of heredity was expected to afford significant control over phenotypic traits. Some studies of inheritance in Morgan's laboratory derived from the aims of eugenics – a form of control over human phenotypic traits. Hermann Muller, a student of Thomas Hunt Morgan's, wrote in his Pilgrim Trust Lecture that the gene is "...a relatively stable controlling structure, to which the rest is attached, and about which it in a sense revolves"(Muller 1947). The focus of his lecture was on self-replication of the gene, and he acknowledged the complex interaction of gene effects with other factors in the production of characters in organisms. But Muller had speculated in 1927 that artificial transmutation — his method of inducing mutations via X-rays — would afford control over human traits (Muller 1927). At the time he considered it too early to say much about using knowledge of genetics toward the aims of eugenics, but by the time of his Pilgrim Trust lecture, he was confident about the potential for control over intelligence (Muller 1947). Because of his theoretical commitment to genes as a relatively stable controlling structure, the (albeit speculative) extension of knowledge from genetics to the control of phenotypic traits did not wait for technology to intervene directly on the mechanisms of gene action.

Further, even before the development of technology to intervene on gene action, gene action itself was a target of classical geneticists. Scott F. Gilbert and Jane Maienschein have emphasized the importance of embryological phenomena for classical geneticists, including Morgan himself, who was originally an embryologist (Gilbert 1978; Maienschein 1984). Gilbert ties Morgan's initial resistance to the chromosomal theory of inheritance to his theoretical commitments in embryology. Maienschein emphasizes that Morgan developed his work on sex chromosomes against the background of embryological investigations into sex determination.

Morgan's work represented a shift from studying the developmental mechanisms of sex determination to the inheritance of sex, but Maienschein shows that by 1911 Morgan was drawing conclusions from inheritance to sex determination itself. Maienschein and Gilbert, therefore, shows an influence of embryological explanatory targets on the development of gene theory. These, again, did not wait for the technology that exploits the specificity of gene sequence to take such targets under investigative scope and intended explanatory scope. The role of gene sequence specificity in protein synthesis has indeed turned out to be a fruitful tool in studies of growth and development, but gene centrism cannot be attributed to the utility of genes themselves.

And third, specificity itself is conceptually precedented as a useful or desirable feature, even though it meant something quite different. It is well-known that the concept of specificity was substantially revised from its stereochemical definition to the informational concept of sequence specificity (P. Griffiths and Stotz 2013). Though it was more of an explanatory target itself than an important causal property, this prior framework of specificity structured much of the work in biochemistry and molecular biology that preceded molecular genetics (Morange 1998; 2020). The existing framework of specificity scaffolded the search for an exploitation of sequence specificity.

The preceding historical discussion suggests that we should view gene centrism as explained more by its history than by specificity as a special causal property. Though specificity is sometimes explanatorily relevant for targets proximate to DNA sequence, and it has a role in the development of genetic technology, it has less and less of a role in accounting for gene centrism as it extends to targets downstream of DNA sequence. Gene centrism depends on the framework that has been set up by those proximate investigations.

This brings us back to the relationship between the objective and pragmatic dimensions of causal selection. Recall that once explanatory aims are set, the criteria for causal selection should be an intrinsic feature of the cause that serves the explanatory aim. But explanatory aims depend on the framework of investigation available – when specificity, particularly sequence specificity of DNA is available to exploit, our explanatory aims are influenced by this availability. Then it is not the case that explanatory aims are independently set first and then tell us what causal properties to prefer. The objective dimension of causal selection is not *independent* of our explanatory aims. Rather, the two are *interdependent*. It is not the case that there is an objective property that happens to be good for our pragmatic goals. Rather, our pragmatic goals are partially determined by the availability of that objective feature. Our explanatory aims were affected by the discovery that some genes were specific for certain effects.

Further support for this claim can be found in Marcel Weber's responses to Waters. Marcel Weber argues that specificity alone does not single out genes in explanation; rather, an additional, precisely defined criterion of *biological normality* is required to sort out which specific actual difference makers matter for explanation and which do not (Weber 2017b; 2017a). The relevant causes are accessible via biologically normal

interventions. These are interventions in Woodward's sense, with two additional criteria:

> (1) the intervention may also be due to natural processes such as spontaneous mutation, replication error, transposition, etc. (the cetera includes all known natural causes of genetic variation)
> (2) the intervention is compatible with the continued persistence of the biological entity that is being considered (Weber 2017a).

That is to say, in order to single out genetic causes as uniquely explanatory, we need a criterion of causal *relevance*. Once defined, we should be able to apply the criterion of biological normality across explanatory contexts. However, Janella Baxter responds to Weber by arguing that geneticists often pursue decidedly *abnormal* interventions in the laboratory, and it is often these that produce new genetic technologies (Baxter 2019). The causal variables manipulated by these abnormal interventions are both useful and explanatory. Here, we can see that the 'objective' feature of biological normality is dependent upon the experimental framework that geneticists develop.

If a variety of historical factors explains gene centrism and the fact that successful explanations in genetics often feature specific causes, and these are the explanations that we search in order to develop causal selection solutions, then we are subject to a kind of sampling bias. If the research choices are constrained by tools that take advantage of specificity, then we should expect explanations (both successful and not) of targets whose causes can be accessed via that tool. For far downstream targets, this may only be a small subset of the things we might otherwise be interested in explaining. We cannot examine successful explanations that we do not have. The real connection between causal selection and gene centrism is not that the properties underlying causal selection will explain gene centrism, but rather that the explanation for gene centrism also explains the solutions to causal selection.

4. Conclusions

What are the consequences for the two questions we started with – the basis for causal selection and the justification for gene centrism? Though specificity is important for causal selection in some contexts, it becomes less relevant for causal selection in explaining phenomena far downstream of DNA. This reveals a limitation

in how far specificity can go in justifying gene centrism, which certainly includes downstream targets within its scope. The other conclusion is a consequence relevant to causal selection in general – it is simply that we must be careful not to overgeneralize when mining successful explanations in biology for solutions to causal selection. This sample is partially determined by the explanatory aims of biologists, which are not independent of causal properties. And so the connection between causal selection and gene centrism is, in a sense, in the opposite direction than philosophers expected. It is not that the properties underlying causal selection will account for gene centrism, but rather that the presence and pervasiveness of gene centrism explains why we have identified particularly those solutions to causal selection.

In contrast to Gannett, I have not argued that gene centrism is unjustified or capricious. She claimed that environmental factors have "perceived unwieldiness" which seems to suggest there is some kind of error in scientists' assessment. But if geneticists have the framework set up to investigate things genetically, it really is "wieldy" to investigate them genetically. It seems more accurate to say that our sophisticated understanding of genes is a product of the framework of genetic knowledge and technology, rather than that biologists perceive them as inherently more amenable to technological control. This idea that causal properties are limited in their ability to explain the success of the genetic approach is broadly consistent with Waters' other views about pluralism and the varied roles of genes in biology. Genes may have been useful handles for the very proximate targets, but they are, on their own, less useful for downstream ones.

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