**Causal selection in context: explaining gene centrism**

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**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 accounting for the popularity of 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 causal 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 causal 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**

It is now uncontroversial that the growth and development of organisms is brought about by the complex interaction of many genetic and environmental factors. But this "interactionist consensus" has opened further questions in the explanation of development – even though both genetic and environmental factors are causally relevant, there is plenty of room for important distinctions among those causes, and these differences have implications for explanatory practice. Further, genetics has been a hugely influential and productive research program, whereas the influence of environmental (or simply non-genetic) factors has received less attention overall and their investigation plays 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, as opposed to a central organizing theory (Waters 2006).

It is reasonable, then, to think that there might be something that distinguishes genetic causes from other causes of growth and development, 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 causal factors, then that special feature could also 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 special feature of genes and its explanatory significance could form a nonarbitrary 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 concept of *fine-grained causal specificity* – do relatively little to account for the success and persistence of genetics. Further, I argue that there is an important dependence in the opposite direction: the success and persistence of genetics helps to explain why we have identified fine-grained causal 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 reasons, and they look for features of causes that make them valuable by our existing explanatory standards. They then typically extrapolate – on this view, finding causes in successful explanations with a particular property is evidence that the property is intrinsically valuable to our explanatory aims. One such property is fine-grained causal specificity (hereafter "causal specificity"). A maximally specific cause is one which takes several states, and for each distinct state of the cause, one or close to one distinct effect state is produced (Waters 2007). This notion of specificity was introduced as both a criterion for causal selection and a justification for gene centrism.[1] I will argue that the prevalence of causal specificity in genetic explanations does not show that it has intrinsic explanatory value. Rather, what it shows is more historical – the success of genetics is fueled by many epistemic, technological, and sociological factors. These factors together produce the available sample of successful biological explanations, from which causal specificity is then extracted as the criterion for causal selection. Put another way, causal specificity appears explanatorily important because other, non-epistemic factors have produced a biased sample of successful explanations in which causally specific genetic factors are overrepresented. From this observation I draw two conclusions. First, the success of genetics as a research program explains the prevalence of causal specificity as a criterion of causal selection. The second conclusion relates to the philosophical practice of identifying causal selection criteria: 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.

I structure the paper as follows: in Section 1, I show how causal specificity is related to gene centrism through the problem of causal selection. In Section 2, I argue

[1] As we will see, fine-grained causal specificity is not the only concept of specificity that plays an important role in this context.

that to understand the relationship between gene centrism and causal specificity, we need to 'zoom out' to explanatory targets that are much further causally downstream from the DNA sequence – the developed traits of organisms. I discuss some responses to Waters' notion of fine-grained causal specificity in the proximate, intracellular environment, and then give several examples at the level of the developed trait that help to separate causal specificity from the selected causes in biological explanations. I conclude that causal specificity, via causal selection, cannot do much to account for gene centrism. In Section 3, I consider the possibility that causal specificity might underlie the utility of genes as tools and argue that it does not. Section 4 concludes.

**1. Connecting Causal Selection to Gene Centrism**

There are two connections between the explanatory process of causal selection and the research program of 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 hand, philosophers have taken the properties identified in those criteria to constitute an important distinction between genetic and non-genetic causes, thus helping to justify gene centrism.

The general problem of causal selection arises for any account of causal explanation. In particular, on a minimal interventionist account like that of James Woodward, no effect truly has a single cause (Woodward 2003). If causes explain their effects, it should follow that each cause features equally and necessarily in the explanation of some effect. 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 dropped on the forest floor may cause a fire, but the presence of oxygen in the surrounding air is just as necessary (Hart and Honoré 1959). But intuitively, it is the dropped cigarette, not the oxygen, that explains the presence of the fire. This case is usually resolved by appealing to a notion of structuring versus triggering causes – the oxygen is, in an important sense, in the background (c.f. Mackie 1974; Dretske 1988; 2004). But is there an intrinsic property that distinguishes these types of cause (or other types) that can be systematically applied across contexts to determine which causes are explanatorily relevant in a non-arbitrary way? If so, causal selection is *principled* in that it is governed by the explanatory value of those properties, and not our idiosyncratic interest in the particular identity of certain causes. Where should philosophers look to find such a causal property?

Biological systems are extraordinarily complex, so they provide many examples of successful explanation despite high causal complexity. This makes them, in the words of Laura Franklin-Hall, a "gold mine for those wanting to identify the selective patterns to which a philosophical account [of causal selection] is responsible" (Franklin-Hall 2015, 18). In her view, searching successful causal explanations is the best way to identify causal selection criteria, and biological explanations offer a good sample. As I emphasized above, contemporary philosophers are interested in finding

causal selection criteria that are based on some intrinsic feature that only some causes have, rather than an arbitrary criterion that only reflects the idiosyncratic interests of some scientists. 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 so it will always be pragmatic in some sense. But if scientists prefer one cause over another for the purposes of explanation simply because they have an idiosyncratic preference for one, then causal selection is not only pragmatic but *capricious*. Lauren Ross has pointed out that there is slippage in the literature between the inevitably pragmatic nature of causal selection and the more problematic charge 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 but also depends upon the interests of investigators (Ross 2019, 3). 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 the distinction between capricious and principled causal selection is relevant to its connection to gene centrism. It could be that there is some intrinsic property of genes (namely, causal specificity) that supplies the objective component to causal selection. This would mean that if scientists prefer genetic explanations, they do not do so arbitrarily. If causal selection of genes is capricious, though, we should hardly expect its capricious underpinnings to justify gene centrism. To be clear, no one expects to find a causal property of genes so valuable that it eclipses all other reasons for the success and persistence of genetic research. But it is reasonable to ask whether there is some relationship between their causal properties and scientific success, and indeed those authors who have investigated causal specificity as a property typically draw some implications in this direction. A prominent example comes from Waters (2007). He introduces the concepts of actual difference making and causal specificity to address both the problem of causal selection and a related version of the parity thesis of Developmental Systems Theory (DST). Waters interprets the DST parity thesis 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).[2] Waters argues that there is a feature of genes that we can point to in order to

[2] Waters appears to draw this interpretation of 'parity' primarily from *Cycles of Contingency* ((Waters 2007, 3; Oyama, Griffiths, and Gray 2003). Oyama and Griffiths have separately responded to the persistent interpretation of DST parity as Millean parity. Griffiths maintains that there is a limited 'parity thesis' stating the symmetry of causal information among genes, environmental factors, and phenotype (c.f., (Griffiths and Stotz 2013)), while Griffiths, Oyama, and Gray elsewhere describe the parity thesis as a rejection of a dichotomy between genes and environment – that such a division is only one possible division, helpful in some cases and not necessarily in others (Oyama 1998; Oyama et al. 2001). Waters' interpretation here therefore simplifies the DST parity thesis. But it does motivate the idea of distinctions among *causal properties*, not only among the identities of different causes, and if

distinguish genetic causes from the others, and he suggests that this feature "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 that genes are the specific actual difference makers in development (Waters 2007). Waters frames these notions within Woodward's interventionist causal framework, in which causes and effects are represented as variables that are systematically related to one another under intervention on the causal variable (Woodward 2003). 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. Waters argues that DNA sequence is an actual difference maker with respect to mRNA sequence in the process of transcription in protein synthesis. In contrast, the enzyme RNA polymerase (a feature of the cellular environment) is only a potential difference maker with respect to mRNA sequence. It is always present in the cellular environment, so even though an intervention to vary its presence or character *would* affect the mRNA sequence, no such variation occurs in typical cells.

The fact that genes alone among the many other causes present 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. In cases in which there are multiple actual difference makers, as there are in protein synthesis in eukaryotic cells, Waters contends that DNA has the further property of fine-grained causal specificity. Waters articulates this notion of causal specificity by combining features from David Lewis's account of causal influence and Woodward's account of causal explanation: in a causal relationship in which $X$ causes $Y$, $X$ has fine-grained causal specificity if it takes many finely incremented values, and these values produce correspondingly fine differences in the value of $Y$ (Lewis 2000; Woodward 2003; Waters 2007). DNA is a causally 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 idiosyncratic preference for one of several equivalent members of the same ontological category, we can say that causal selection of genetic causes is principled. For Waters, causal selection is principled in general, and in particular, it is principled in the case of genes as causes of growth and development. Further, he argues that actual difference making, together with causal

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DNA does have a particularly valuable property, this does challenge the claim that the gene-environment division is only one of many choices of equal explanatory potential.

specificity, underlies the selection of genetic causes in explanations of growth and development. 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 causal specificity) and a pragmatic side (our preexisting explanatory aims to which actual difference making and specificity are well-suited).

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 biomedicine. In this strong version of an argument against principled causal selection, Gannett argues 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 argues that this belief comes from the "perceived unwieldiness" of environmental factors and an avoidance of complex problems (Gannett 1999, 370). The reasons for singling out genes as particularly explanatory have to do with the extra-scientific goals and preferences of the scientists involved, rather than any intrinsic features of genes as causes. On Gannett's view, there is no objective criterion of causal selection for biologists to systematically apply once they have specified an explanatory target.

In general, philosophers of biology have resisted strong claims of capriciousness like Gannett's. Waters' view that causal specificity is a significant property of genes is taken to be the received view among philosophers (Planer 2015; Griffiths and Stotz 2013; Neal 2019; Weber 2017b). Further, other concepts of specificity are extremely influential in other parts of the philosophy of causation (Griffiths et al. 2015). So, while no one believes that causal 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 causal specificity provide the objective dimension of causal selection in explanations 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 causal specificity is identified as important for causal selection, and thus that the objective and pragmatic components of principled causal selection, though conceptually separable, are interdependent. These insights limit the generalizations about causal selection that we can make from successful biological explanations, but they do not necessarily lead to an extreme view like Gannett's.

## 2. Causal Specificity: The Objective Dimension of Causal Selection?

In this section, I discuss several examples in which Waters' notion of causal specificity either fails to identify the selected genetic cause in a biological explanation, or it successfully identifies the selected cause, but that cause is not genetic. One might object that the fact that some selected causes are not specific, or are specific but not genetic, is not relevant. For example, Janella Baxter argues that to present counterexamples as objections to the scope of actual difference making and causal 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 parity thesis as Millean parity and therefore identifying the parity thesis with the general philosophical problem of causal selection. Recall that Waters makes clear that his aim is not only 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 account for gene centrism. Actual difference making and specificity are neither unique to DNA nor a ubiquitous property of selected causes in growth and development. And the extent to which causal specificity accounts for gene centrism *does* depend on how often DNA actually exhibits causal specificity in successful explanations.

To this end, I will discuss explanatory targets of varying proximity to DNA sequence to show that causal specificity and causal selection come apart in explanations of growth and development. Waters uses examples from the immediate intracellular environment to argue for actual difference making and causal specificity. This explanatory target is proximate to DNA sequence 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. In contrast to 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 proximate cellular environment of DNA molecules.[3] And so I will discuss examples from the intracellular environment, the slightly 'zoomed out' environment of gene expression in, e.g., tissues, and finally to the developed phenotypic trait. Traits are the focus of the paradigmatic works of DST, which are some of Waters' primary targets (e.g., Oyama et al. (2001), Oyama (1998), Griffiths and Gray (1994)) and notably they are also the original target

[3] Waters, more recently, points out that genetic explanations that rely on causal 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).

of the study of heredity, as some biologists have recently pointed out, e.g., Orgogozo, Morizot, and Martin (2015)).

*2.1 Proximate processes: protein synthesis and gene expression*

Within a broader argument for a different conception of specificity in genetics, Paul Griffiths and Karola Stotz provide reason to think that DNA exhibits Waters-style causal specificity in relatively few contexts within cells (Griffiths and Stotz 2013). They argue that DNA is not the "sole source of specificity" for gene products (Griffiths and Stotz 2013, 78). Griffiths and Stotz aim to clarify the role and character of specificity in biological development. Their argument is a broader presentation of specificity in genetics but is aimed partly at Waters. They begin with a reconceptualization of the gene in modern biology – the *postgenomic gene*, identified not by particular segments of DNA at particular loci but by the "collection of sequence elements" that collaborate to build a functional product (Griffiths and Stotz 2013, 75). They present specificity is a feature of the gene product – the sequence of RNA nucleotides in a functional RNA molecule, or the primary structure (amino acid sequence) of functional proteins. These products are instances of an enormous variety of possible sequences. Rather than a relationship between a cause and an effect, specificity, for Griffiths and Stotz, is an explanatory target of its own – what molecular geneticists need to figure out is how the particular identity (sequence) of the gene product is determined. This conception of specificity follows Francis Crick's sequence hypothesis, in which specificity is also treated as a feature of a piece of a nucleic acid (Griffiths and Stotz 2013, 40). Griffiths and Stotz elaborate this within the framework of information science, which, as they show, neatly captures the idea represented in the sequence hypothesis: there is a certain amount of specific information in the gene product, and that information must come from somewhere – precisely *that* information, or else it would be a different product. The sequence specificity of the gene product underlies its specificity in the historical, stereochemical sense: it interacts with only very particular substrates (Griffiths and Stotz 2013, 33–40).

Their foundational claim about specificity is that the information that determines the precise identity of a gene product is not contained within only one contributing causal factor – instead, that information is distributed among many causal factors. To capture this idea, they introduce a concept of *distributed specificity* – the cell can precisely control which gene products are made, but only through the action of several causal factors brought together in the right arrangement. They demonstrate this through a careful examination of the processes by which cells actually build gene products. In these processes it is typical, not exceptional, for cells to use a wide range of regulatory factors to determine the particular sequence of a gene product, including but not limited to *cis*-acting sequences, *trans*-acting regulators, and environmental signals. Cells use this process of "regulated recruitment and combinatorial control,"

not nucleotide-level variation, to control which gene products are produced (Griffiths and Stotz 2013, 49).

The implications of their argument for Waters' notion of causal specificity and its role in causal selection, however, need explication. Griffiths and Stotz intend for their argument to respond directly to Waters. They position Waters as holding essentially the same view as Crick in the sequence hypothesis – on their view, when Waters claims that DNA sequence is the only specific actual-difference maker with respect to gene product, he is claiming that DNA is the "sole source of specificity" for the mRNA sequence (Griffiths and Stotz 2013, 78). But this is a subtle distortion of Waters' view. Waters' notion of causal specificity is a property of causal *relationships*. Distributed specificity, in contrast, does not describe a relationship between any one cause and the effect. On Griffiths and Stotz's view, specificity is a kind of achievement, which the cell uses "combinatorial control" to attain. Specificity is a feature of the product that needs explanation (where does it come from? how is it achieved?), not a feature of a causal relationship that produces it. Waters' notion of causal specificity is a property of the mapping between a causal variable and an effect variable; on his view it is incoherent to say that there is a "source" for causal specificity. The Waters picture would certainly allow that many factors contribute to the *particular* identity of a gene product, but he would maintain that only (or most often), DNA sequence is the only cause that has this special relationship of fine-grained specificity with respect to the product. Griffiths and Stotz are, for the most part, making a positive claim by means of their conceptual shift in 'specificity' — theirs is the specificity that matters, because Waters' causal specificity does not feature in the typical activity of cells. But at some points they equivocate, rather than shift. For example, shortly after claiming that the specificity of a gene product is distributed among "*cis*-acting sequences, *trans*-acting regulators, environmental signals, and contingent history of the cell," they claim that "…all the factors just listed are causally specific difference makers" (Griffiths and Stotz 2013, 99). This is not so — none of these is necessarily a causally specific difference maker. In fact, each of these may have varying degrees of *causal* specificity with respect to the sequence gene products, depending on the product of interest. These factors may have relatively few states that correspond to relatively few differences in the gene product, which is only to the cell's benefit, if that is the sort of control required to produce the product in question.

Contrary to their stated aims, however, they do not show that there exist other *causally* specific actual difference makers in protein synthesis; they instead show that there often are no causally specific actual difference makers to be found, because there are not particular causal factors that 'concentrate' variation into one factor (it is instead distributed among many). Griffiths and Stotz show convincingly that cells do not typically achieve the particular identities of their gene products by modulating the nucleotide sequence and instead do so by recruiting different sets of causal factors (regulated recruitment and combinatorial control); which does imply that the cell is

not exploiting the causally specific relationship between DNA and RNA sequence to regularly produce the actual variety of gene products that it produces. More accurately, then, they show that there typically *are no* specific causes for the gene product.[4] We will return to Griffiths and Stotz's concept of distributed specificity in Section 3, but the negative conclusion that cells do not typically exploit DNA sequence variation in the way that Waters claims is important for our purposes here, because it implies that the causes selected in explanations of biological development at the intracellular level are not governed by causal specificity. Some arguments against causal specificity in proximate processes extend beyond protein synthesis; other philosophers have made claims similar to those of Griffiths and Stotz about broader gene regulatory networks (DiFrisco and Jaeger 2020). It will be helpful, however, to consider further cases that support the separation of causal specificity, causal selection, and genetic causes.

### *2.3 Phenotypic traits*

Another argument that extends from proximate contexts to more distal ones comes from Janella Baxter, who argues that gene *expression levels*, not DNA sequence, control phenotypes at the proximity of tissues and beyond, and these are *often* the relevant feature for causal selection in explanations of developmental biology. Gene expression level, however, might have fine-grained control over a phenotype, but it might instead have a threshold effect (Baxter 2021). Gene *knockdown* experiments finely modulate the level of a gene's expression, while gene *knockout* experiments prevent its expression entirely. This latter type of control is not causally specific in Waters' sense. In the sections that follow, I will give several examples that help to decouple causal specificity from genetic causes in growth and development by considering explanatory targets causally far downstream of DNA sequence.

#### *2.3.1 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 causal specificity.

Griffiths and Stotz (2013) use developmental plasticity as an example to demonstrate that environmental factors can be present among the causes of a developmental outcome – they characterize it as one of the locations of distributed specificity. But again, this is to say that an environmental factor is one of the causes of the particular identity of the gene product; it does not necessarily mean that the environmental factor is itself a cause with fine-grained specificity. On their view,

[4] Planer (2015) makes another observation along these lines but does not pursue implications for Waters' account.

environmental factors may be binary switches and yet maintain their membership to the "distributed specificity" of the gene product. Because the example I give here describes a continuous, dosage-dependent morphological response to an environmental factor, it shows that an environmental factor – a single causal variable – can have fine-grained specificity of just the same kind that Waters attributes to DNA sequence.

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," 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.

*2.3.2. 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 to break down those substances.

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. Taken together, these cases help to complete the separation of causal 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 causal 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 causal specificity as a criterion for causal selection and 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). Recall that Griffiths and Stotz intended to replace Waters' notion of causal specificity with the information-based notion of distributed specificity. But if Waters views causal specificity as explanatorily important because it is useful, its utility depends crucially on just this feature of the concept: that causal specificity is a feature of the relationship between *one causal variable* and an effect variable.

But what makes genes useful? Perhaps causal 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, causal 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 causal 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 causal specificity, though not always. They do typically exploit the complementarity of DNA and RNA strands. But they do not always exploit *causal 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 causal specificity of the DNA sequence with respect to the RNA product identity. Of course, he is right that a wide range of important tools have been developed that exploit the causal specificity of the DNA sequence – but as Griffiths and Stotz showed, the modern concept of the gene is not really localized to segments of DNA sequence, but rather characterized by functional groupings of DNA segments and regulatory factors. It is more accurate to say that *complementarity,* rather than *genes,* is a useful tool – because that is what has allowed us to build the technology of molecular genetics. And complementarity has been useful because it constitutes a causally specific relationship between DNA and RNA sequence. In the right laboratory environments, DNA is a causally specific actual-difference maker for RNA sequence.

Second, like any tool, genes (or complementary base-pairs) are not useful solely because of their properties, but because we have the means to take advantage of those properties. Even if causal 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 causal specificity's role in causal selection, causal specificity cannot explain *why* so many

explanatory targets – even those which are 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 causal 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 Thomas Hunt Morgan's laboratory derived from the aims of eugenics – a form of control over human phenotypic traits. Hermann Muller, a student of 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 already 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 causal specificity of gene sequence to take such targets under investigative scope and intended explanatory scope. The role of causal specificity in limited contexts of 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. The concept of specificity was substantially revised from its stereochemical definition to the informational concept of sequence specificity when Crick introduced the sequence hypothesis (Griffiths and Stotz 2013). This prior framework of specificity structured much of the work in biochemistry and molecular biology that preceded molecular genetics, in which biologists sought to understand how biomolecules managed to take such particular forms that they could only react with one or a few substrates (Morange 1998; 2020). Because specificity was already a highly salient property expected to yield far-reaching understanding of biological systems, this existing framework of stereochemical specificity likely 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 causal 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 criterion 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 causal specificity (in the complementary relationship between DNA and RNA) strands 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. Moving from a causal property like causal specificity to the conclusion that it is explanatorily significant implicitly invokes the idea that what we can access is explanatorily significant for our aims – maybe it is reasonable or otherwise acceptable that our explanatory ideals depend in part on what we can access, but it does not imply inherent epistemic superiority.

Further support for this claim can be found in Marcel Weber's responses to Waters. Marcel Weber argues that causal 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 causal specificity, then we should expect explanations 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 causal 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 causal 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. Therefore, 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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