The genotype–phenotype distinction: from Mendelian genetics to 21st century biology

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Abstract

The Genotype-Phenotype (G-P) distinction was proposed in the context of Mendelian genetics, in the wake of late 19th century studies about heredity. In this paper, we provide a conceptual analysis that highlights that the G-P distinction was grounded on three pillars: observability, transmissibility, and causality. Originally, the genotype is the non-observable and transmissible cause of the phenotype, which is its observable and non-transmissible effect. We argue that the current developments of biology have called the validity of such pillars into question. First, molecular biology has unveiled the putative material substrate of the genotype (*qua* DNA), making it an observable object. Second, numerous findings on non-genetic heredity suggest that some phenotypic traits can be directly transmitted. Third, recent organicist approaches to biological phenomena have emphasized the reciprocal causality between parts of a biological system, which notably applies to the relations between genotypes and phenotypes. As a consequence, we submit that the G-P distinction has lost its general validity, although it can still apply to specific situations. This calls for forging new frameworks and concepts to better describe heredity and development.

Keywords

Mendelian genetics - Epistemology - Molecular biology - Extended heredity - Epigenetics - Organicism

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GP wrote the first draft, and all authors participated in substantial discussions and revisions to the manuscript.

It is a well-established fact that language is not only our servant, when we wish to express–or even to conceal–our thoughts, but that it may also be our 3, overpowering us by means of the notions attached to the current words. This fact is the reason why it is desirable to create a new terminology in all cases where new or revised conceptions are being developed. Old terms are mostly compromised by their application in antiquated or erroneous theories and systems, from which they carry splinters of inadequate ideas, not always harmless to the developing insight. (Johannsen, 1911, p. 132)

1. Introduction

The theoretical distinction between "genotype" and "phenotype" was a structuring one in 20th century biology. It was famously proposed by the botanist Johannsen (1909, 1911) in the context of the developing Mendelian genetics, the new science of heredity which was elaborated further to the rediscovery of Mendel laws by de Vries, Correns and Von Tchermak (Fox Keller, 2000, p. 1; Gayon, 1992, p. 281). To Johannsen, the genotype referred to the sum of inherited genes, while the phenotype designated "types" of organisms that could be measured and described. In this view, the "like-begets-like" phenomenon – namely heredity – came to be explained by the fact that parents and offspring bore the same genotype.

Today, the distinction between genotype and phenotype (hereafter: G-P distinction) is still widely employed in the discourse of biologists. Yet, when considering the evolution of biological knowledge, one might ponder the extent to which the distinction remains relevant for contemporary biology. While the evolution of the concept of gene has been the subject of many studies (Portin, 1993; Fox Keller, 2000; Gayon, 2004; Griffiths and Stotz, 2013), the conceptual work dedicated to the G-P distinction has been more limited, and mostly focused on the complexity of the so-called "genotype-phenotype mapping" (see for example Alberch, 1991; Lewontin, 1992; Orgogozo et al., 2015). Here, we examine the theoretical validity of the G-P distinction. We argue that the distinction is no longer able to make sense of biological phenomena *in general,* although it is still applicable in specific cases. Our conceptual analysis leads us to suggest going beyond the G-P distinction and adopting new concepts elaborated from within an organizational theoretical framework.

The argument is organized as follows. In section 2, we address the context in which the G-P distinction was elaborated. We show that this distinction places itself in the wake of the 19th century's separation between hereditary germs and hereditary traits, and we recall how it was formalized by Mendelian genetics. We highlight more specifically that the G-P distinction is grounded on the theoretical distinction between factors and traits (both involved in heredity), which are supposed to be, respectively: i) non-observable and observable ii) transmissible and non-transmissible iii) causal and epiphenomenal (i.e. mere effects). In section 3, we analyze the scientific advances that have weakened each of these three pillars and, consequently, the relevance of the very G-P distinction. In particular, we argue that i) the development of molecular genetics has undermined the distinction between non-observable genotypes and observable phenotypes, ii) the concept of extended heredity implies that both genotypes and phenotypes can be transmitted to offspring, and iii) the systemic-organicist theoretical framework, currently the object of a growing attention, emphasizes that genotypes

and phenotypes co-determine each other. In section 4, we examine some implications and possible objections to our argument, and we finally suggest that the G-P distinction might be replaced by original conceptual tools, more appropriate to make sense of recent discoveries on biological phenomena.

2. Nucleating the G-P distinction

The distinction between genotype and phenotype emerged with Mendelian genetics, at a time when studies about biological heredity started being institutionalized. In this section, we recall that this distinction places itself in the wake of earlier studies developed in the 19th century, before explaining how it was elaborated at the beginning of the 20th century.

2.1. The concepts before the words in 19th century biology

Biological heredity broadly refers to the "like-begets-like" phenomenon (Darwin, 1859), namely to the passing of traits across generations through reproduction (Müller-Wille and Rheinberger, 2007). While the fact that offspring tend to look like their parents has been noticed since Antiquity, the first conceptual and theoretical studies about biological heredity did not arise before the 19th century. It is only then, indeed, that heredity started referring to specific causes producing a specific set of phenomena (López-Beltrán, 1994; Bowler, 2001).

At the time, it was thought that a good theory of heredity should explain not only the transmission of individual and species traits (parent-offspring similarities) and hybridization (combination of parental traits), but also the irregularities observed in the transmission of features (Darwin, 1868; Galton, 1876; Weismann, 1883; Spencer, 1864). Indeed, offspring do not necessarily resemble their parents, some characters can reappear after one or several generations (reversion) and children born from the same parents are not identical.

Many conceptions of heredity developed in the 19th century[1] suggested that while heredity refers broadly speaking to the fact that parents transmit observable traits to their offspring, it designates *stricto sensu* the transmission of elements which are not the traits themselves, but underlying "germs" that can develop (or not) into observable traits, generation after generation. This distinction between traits and germs (soon to be called "factors") was to be expressed in diverse ways.

Darwin, whose work on evolution required the nucleation of a concept of heredity, distinguished between the germs and the developed parts of the body (Darwin, 1868; 1871; Galton, 1876; Johannsen 1911, p. 129-130; Gayon and Petit, 2018, p. 306-307). To him, germs were made of "gemmules", that is, elements expelled by the body's organic units all along ontogenesis (a hypothetical process he called the 'pangenesis'). Gemmules could therefore be mapped onto these body parts. However, they could be transmitted across generations without being developed. This partial decoupling between trait transmission (heredity) and trait development (ontogenesis) was consistent with the fact that some traits could be transmitted in a latent form. Reciprocally, Darwin's theory retained the possibility

[1]Two conceptions of heredity can be distinguished in the 19th century: a phenomenal (statistical) one, according to which heredity is merely a measurable resemblance, and a physiological one, which interprets heredity as a process of material transmission (Gayon, 1992; 2000). The phenomenal approach only measures resemblances between parents and offspring without any consideration for underlying processes. In this paper, we leave it aside.

of directly transmitting acquired traits to offspring, a possibility that so-called Neo-Darwinians (see Romanes, 1888) would later call into question (Bowler, 2001). Weismann, at the forefront of Neo-Darwinism, sought to clearly distinguish between the characters and their determinants, which he thought were of a different nature (Weismann, 1904, p. 107-8). From cytological observations, he distinguished the "germen" – that ensures the continuity across generations – and the soma – the body parts of parents and offspring (Weismann, 1883). To him, somatic and germ cell lineages separate early during ontogenesis and the germen determines parents and offspring traits (in such a way that what happens during the parent's life does not impact the offspring's germen and soma – at least not in a significant, directed way; see Weismann, 1893, pp. 411-422). A few years earlier, Galton had stated, in a similar vein, that "our own embryos (...) have sprung immediately from those embryos whence our parents were developed" (1865, p. 322). He had distinguished the *stirps* – the sum of germs transmitted across generations – and the personal organism – which was an imperfect representation of the former (1876). In his view, the stirps of an individual contained more germs than those that would be developed during ontogenesis (Galton, 1876, p. 199). This explained why an individual could pass on a trait – like some genius skills or a disease – that she did not exhibit herself (Galton, 1872, p. 395).

2.2. Mendelian genetics

At the turn of the 20th century, de Vries, Correns and von Tschermak simultaneously rediscovered the Mendelian laws which would found the new science of heredity, soon to be coined 'genetics' (Gayon, 2004; Fox Keller, 2000; Bowler, 2001). These laws, which initially concerned the "formation and development of hybrids" (behavior of traits in hybrid offspring), were elaborated further to a series of experiments on peas and recorded in Mendel 1865's essay.

The first law, that of segregation (or purity of gametes), refers to the "separation of pairs of opposite characters in sexual cells" (Lenay, 1990, p. 5). The second law, that of "independent disjunction of characters", states that different pairs of characters have an independent behavior (Lenay, 1990, p. 5). Mendel distinguished between "pure" (a; A) and "hybrid" (aA) characters, but also between "dominant" and "recessive" ones. Dominant characters were thought to be passed on to descendants, while recessive characters were supposed to be latent in hybrids, and to possibly reappear in the descendants. Like Galton and Weismann, Mendel distinguished between what is transmitted and what is observed across generations, insofar as he made a distinction between the "exterior" and the "intimate structure" of plants: "Gregor Mendel's scheme required the existence within organisms and their gametes of unobserved entities, hereditary factors (...), whose state was not in a one-to-one correspondence with the appearance of the organisms themselves" (Lewontin, 1992). Finally, the rediscovery of Mendelian laws allowed scientists to consider heredity, which had appeared as a versatile force for a long time, as a phenomenon obeying specific rules, providing the foundation for a new discipline, that of Mendelian genetics, focusing on the transmission of traits between generations. The nucleation of Mendelian genetics came with the elaboration of a host of new theoretical terms such as allele, homo/heterozygote (Bateson, 1902), as well as the distinction between genotype and phenotype. The latter, along with the concept of "gene", was coined by the Danish botanist Wilhelm Johannsen (1909, 1911), to whom the new science of heredity should rely on a clear conceptual language if it were to depart from older and erroneous conceptions.

The word *gene* designated the "unit-factors" that are present in the gametes and whose existence had been "demonstrated by recent Mendelian researches" (Johannsen, 1911). Constructed from the word "pangene" proposed by de Vries (after Darwin's 'pangenesis') to designate intracellular organelles (de Vries, 1889), it referred to theoretical and functional elements which were not directly observable but merely knowable through their effects on the phenotype (Gayon, 2004). Although to some such unobservability was plausibly to be only temporary -- the 1900s were the time whence the chromosome theory of heredity started burgeoning (Sutton, 1903; Boveri, 1904) -- not all early actors of classical genetics would be inclined to interpret genes as material particles (Bowler, 2001, pp. 120-137). For Johannsen for instance, the gene was "forever unobservable and probably consisted of stable energy-states within the organism as a whole" (Bowler, 2001, p. 124). Thus, Johannsen refrained from making any speculative hypothesis on the physical nature of these units (Gayon and Petit, 2018, p. 308; see Johannsen 1911, pp. 131-3). The gene, in this context, appeared as "a *tool* for predicting the outcome of breeding one organism with another" (Griffiths and Stotz, 2013, p. 15, their emphasis), it "typically correspond[ed] to what philosophers of science call a 'theoretical entity' (...) an entity that cannot be directly described from observables" (Gayon, 2004). The *genotype* designated the sum of genes present in the gamete or the zygote. Just like the genes that composed them, genotypes were not directly observable but "[could] be examined only by the qualities and reactions of the organisms in question" (Johannsen, 1911, p. 133). The *phenotype*, in turn, referred to "types of organisms", "distinguishable by direct inspection or only by finer methods of measuring or description". It denoted the set of observable traits of the organism.

Johannsen (1911, p. 129) made explicit that the "genotype conception of heredity" radically departed from the "transmission conception" of inheritance (also called phenotype-conception, p. 135), already rejected by Galton and Weismann. According to the transmission conception, heredity (or "natural inheritance") was "realized by (…) the transmission of the parent's (or ancestor's) *personal qualities* to the progeny". In contrast, the genotype conception stated that i) parents do not transmit personal qualities – i.e. apparent traits – to their offspring, but rather some "sexual substances" or the "gametes", and that ii) these gametes determine, but are not determined by, parents and offspring development (Johannsen 1911, p. 130). The genotype conception of heredity thus appears as a vindication of a "hard" (contra "soft") view of inheritance, according to which traits acquired during ontogenesis do not have any influence on what is transmitted to offspring, a view that was a stumbling block in early 20th century biology (Mayr, 1998, p. 15).

2.3. The three pillars of the G-P distinction

The G-P distinction, as proposed in the specific context of Mendelian genetics, rested on the hypothesis according to which hereditary factors and hereditary traits were different in nature (Jacob, 1970, p. 91). We submit more precisely that the distinction between factors and traits relies on three distinct pillars.

First, the G-P distinction relies on the distinction between unobservable hereditary factors and observable hereditary traits (*observability*). Second, it endorses the distinction between transmissible and non-transmissible elements (*transmissibility*). While genes are transmissible, traits are not, and their maintenance across generations depends on genetic transmission. Third, the G-P distinction implies that non-observable transmissible genotypes are the cause of recurring, observable and non-transmissible phenotypes, but not vice-versa

(*causality*). The causal relation between hereditary factors and hereditary traits is therefore meant to be unidirectional (see for instance Maynard Smith, 1958, Fig. 8).

It is worth emphasizing that, from its very inception, the causal relationship between genotype and phenotype is expressed in terms of *differences* making *differences* (Stewart, 2004; De Vienne, this issue; on causality *qua* difference-making see Bernard, 1865; Pearl, 2009; Woodward, 2003). Genotypes are discrete *difference makers* that produce differences in the phenotypes. Mendelian genetics, hence, is first and foremost interested in the transmission of difference-makers.[2]

A consequence of the G-P distinction is that it granted the divorce between trait transmission (heredity) and trait development (ontogenesis) (Lewontin, 1992), a divorce that was already in germ in the 19th century's contributions (Bowler, 2001, p. 127). Even if it was "essentially methodological" (Gayon and Petit, 2018, p. 304-5), the distinction between ontogenesis and heredity was a prerequisite for the development of a science of heredity (Lenay, 1990, p. 7; Morange, 2003, p. 35), and parted with the old idea of "generation" according to which the formation of an individual similar to its parents involves both transmission, reproduction and ontogenesis (Müller-Wille and Rheinberger, 2007, p. 3). The divorce between heredity and development was notably apparent in Morgan's disciplinary separation of genetics, the science of trait transmission, from embryology, the science of trait expression (Bowler, 2001; Gilbert, 2003, p. 81). To be more precise, one could refer to an *asymmetric* dependence of development on heredity (Lewontin, 1992, p. 138; Walsh, 2010, p. 324), because of the unidirectional causal relation between factors and traits. Such an asymmetric dependence was also adopted in evolutionary biology, in the framework of the Modern Synthesis. There, the G-P distinction was intertwined with a conception of evolution as a change in gene frequencies under the effect of natural selection (Dobzhansky, 1937; Mayr, 1961; 1998). In this view, genotypic variation specifies phenotypic variation (but not vice versa), and ontogenesis is irrelevant with regards to evolutionary processes (see Pigliucci, 2010, for an analysis).

3. The G-P distinction fraying

The G-P distinction is still largely employed nowadays. Yet, scientific advances of 20th and 21st centuries' biology have shaken its foundations. In this section, we analyze i) the development of molecular genetics, which led to the materialization and blurring of the gene, ii) the extension of heredity, which led to the idea of phenotypes' transmission and causal role in heredity and evolution; iii) the resurgence of organicist theoretical frameworks, which challenge the neat distinction between causes and effects in biological systems, and the idea of a unidirectional causality from genotype to phenotype.

3.1. Molecular genetics: unveiling the non-observable

As noted above, Mendelian genetics was an instrumentalist science. However, the question of the materiality of hereditary factors had been asked for decades before the establishment of Mendelian genetics, and scientists have kept investigating the physical basis of heredity during the 20th century. The units of heredity have been thought as located on the

[2]This differential view of the genotype-phenotype causal relationship was recently reaffirmed (Orgogozo et al., 2015), notably to prevent naïve interpretations according to which genes alone would be the causes of traits.

chromosomes since the last decades of the 19th century (Gayon et Petit, 2018, p. 321; Falk, 1984, Griffiths and Stotz, 2013, p. 16). In the 1910's and 1920's, Morgan's school developed the first genetic maps related to the chromosomal theory of heredity (Muller, 1922; Morange, 2003). In the 1940's, Avery, Mac Leod and McCarty showed, through experiments on pneumococcus, that the material basis of genes was provided by deoxyribonucleic acids (DNA) and not by proteins (Avery et al., 1944), although their results were first met with skepticism (Bowler, 2001, pp. 171-177), the enzymatic vision of genes being widespread among biologists in the 1940s (Morange 2003, p. 40). In the 1950's, Watson and Crick (1953a; 1953b) unveiled the double helical structure of DNA (see also Franklin and Goslin, 1953; Wilkins et al., 1953), and speculated that genes were composed of a series of nucleotides located on a double strand, providing a template for the synthesis of proteins.

The materialization of the gene challenges the distinction between non-observable factors and observable traits. If genes consist of DNA sequences coding for proteins, they become entities that are directly observable, independently from their effects. To take a statistical analogy, the genotype was originally conceived of as a latent variable; molecular genetics propelled it to the realm of observable variables. As Lewontin (1992, p. 143) put it: "At the lowest level the DNA sequence of the genes itself is a phenotype, and a complete description of the DNA sequence is identical with a complete specification of the genotype". Nowadays, hence, the genotype essentially refers to "some relevant part of the DNA passed to the organism by its parents" (Peter and Lewontin, 2021), while the phenotype designates "the physical and behavioral traits of the organism" (Peter and Lewontin, 2021).

It is important to note that the materialization of the genotype went with the diversification, and even the explosion, of the gene concept (Fox Keller, 2000; Gayon, 2004). In molecular biology, a functional distinction was first made between "structural" and "regulatory" genes (Jacob and Monod, 1961), the former referring to coding units and the latter to regions controlling rates of transcription (Fox Keller, 2000). Later on, the discovery during the 60's and the 70's of fragmented genes, repeated genes, overlapping genes, nested genes, transposable genes, assembled genes, as well as alternative splicing, revealed that genes could not be reduced to linear and spatially bounded DNA sequences and could be (and most of the time are) involved in determining more than one trait, a phenomenon referred to as pleiotropy (Stearns, 2010, p. 770).

Overall, these advances suggested that Mendelian genes (the hereditary units involved in the determination of a trait) do not easily map to molecular genes (the material units) in a univocal way (Pichot, 1993; Fox Keller, 2000; Gayon, 2004), and "dissolved the hope of building a general and univocal concept of gene" (Gayon, 2004, p. 251; see also Portin, 1993, quoted by Fox Keller, 2000, p. 67). This made "the genotype-phenotype mapping" (Alberch, 1991) more complex than expected[3]. In this context, some authors (e.g. Pigliucci, 2010) advocated the necessity to better understand how developmental processes modulate and regulate gene expression, and therefore participate in shaping the link between genes and traits.

Thus, in the context of molecular biology, the genotype has come to designate observable DNA sequences transmitted and differently used by organisms to reconstruct distinct traits across generations, while the phenotype has come to refer to observable traits of organisms (including proteins, cellular machinery, tissues, organs), not transmissible and determined by

[3]The effects of interactions – of genes with other genes (epistasis) and of genes with the environment (norms of reactions) – also increased the complexity of the G-P relations, insofar as they imply a many-to-many relation between the genotype and the phenotype (see Orgogozo et al., 2015; De Vienne, this issue).

DNA sequences. Overall, the findings of molecular biology advocate for a refined description of causal factors in heredity and development, which do not seem to easily map onto Mendelian categories.

3.2. Extended heredity: making the phenotypes transmissible and causal

For the past 40 years, heredity has been widened so as to include, beyond the transmission of DNA, a set of non-genetic mechanisms involved in the recurrence of phenotypes across generations (Jablonka and Lamb, 2005; Bonduriansky and Day, 2018; Danchin et al., 2019). We submit that the extension of heredity tends to restrict the validity of the distinction between transmissible hereditary structures and non-transmissible hereditary traits (and, in parallel, the distinction between causally efficient hereditary factors and epiphenomenal hereditary traits).

What is usually referred to as "non-genetic heredity" notably includes epigenetic, behavioral (cultural), symbiotic and sometimes ecological transmissions (Jablonka and Lamb, 2005; Danchin et al., 2019). Epigenetic transmission refers to the fact that some molecular marks controlling DNA expression (e.g. DNA methylation) can be maintained across cellular divisions, within and across generations of multicellular organisms (Jablonka and Raz, 2009; Richards et al., 2010; Heard and Martiensen, 2014; Joly and Grunau, 2018).[4] Behavioral transmission occurs when offspring reproduce parents' behavior through social interactions (Avital and Jablonka, 2000; Galef and Laland, 2005). Symbiotic transmission refers to the fact that some symbiotic partners can be passed on across generations and perform the same metabolic functions in parents and offspring (Gilbert, Sapp and Tauber, 2012). Ecological inheritance generally designates the persistence of a constructed niche, which can be selective (Odling-Smee, 2010) – when organisms change the selective pressures acting on them and their offspring – or developmental (Stotz, 2008, 2017) – when organisms impact the developmental environment of the next generation. Hormonal transmission can also be considered as a distinct case of non-genetic heredity (Jablonka and Lamb, 2005, p. 146).

That some traits can be directly passed on means that their *actual* presence and manifestation at the parental generation is a necessary condition for their reappearance at the offspring generation, or, in other terms, that the hereditary transmission of these traits is causally underdetermined by other elements (that might also be transmitted, e.g. DNA). For example, in some passerines such as the Mockingbird, a song must be actually sung at one generation for it to be passed on to the next generation (see Lewontin, 1992, p. 144). While the ability to sing might well depend (in part) on the bird's DNA, the precise determination of the song causally depends on its actual presence across generations.

The specific interpretation of extended heredity can be debated (Merlin and Riboli-Sasco, 2017; Pontarotti, 2015) as well as the impact of non-genetic transmission on evolutionary processes (Pocheville, 2019). Yet, extended heredity provides strong support to the idea that biological legacies are not restricted to DNA sequences, and that elements of the parental body can be directly transmitted to offspring (Bonduriansky, 2012, p. 333; Jablonka and Raz,

[4]Trans-generationally inherited epigenetic marks are sometimes referred to as "epigenotypes" (e.g. Hofmeister et al., 2017). We note a similar trajectory of this concept with that of the genotype. Waddington originally coined the term "epigenotype" to mean something rather abstract: "the set of organizers [i.e. genes] and organizing relations" (Waddintgon 1939 [2016]) or, in a slightly different sense, the complex of developmental processes that link the genotype and phenotype (Waddintgon, 1942; see Boisseau, in prep.). The epigenotype came to be interpreted in a molecular way following the development of molecular biology. (Haig, 2012)

2009, p. 133)[5]. In doing so (and in suggesting that some traits can be causally involved in their own recurrence), extended heredity imposes severe limitations on the second pillar of the G-P distinction. Correlatively, it rehabilitates the "phenotype conception" of heredity that was early-on discarded by Johannsen (1911, p. 130), and by Galton and Weismann before him.

Finally, the causal role of phenotypic traits in heredity contributes to weakening the aforementioned divorce between development and heredity. Indeed, the literature about extended heredity suggests that ontogenesis *does* matter for heredity. It notably emphasizes that heredity can be, at least in part, developmentally constructed (Lamm and Jablonka, 2008) and that traits acquired during ontogenesis can be passed on across generations (Jablonka & Lamb, 2005; Bonduriansky, 2012). This suggests that developmental processes are relevant to inheritance processes, and that organismal physiological states should not be considered as epiphenomenal (i.e. deprived of any causal role) when thinking about heredity and evolution (Griesemer, 2000; Danchin and Pocheville, 2014).

3.3. The organicist perspective: from unidirectional to mutual determination

That phenotypic traits play a role in their own intergenerational recurrence does not in itself affect the third pillar of the G-P distinction, which states the unidirectional determination from the genotype to the phenotype. The genotype can still be conceptualized as a set of transmissible elements that contribute to determining the other organismal elements, *but not vice-versa*. Yet, there is a family of senses in which phenotypes play a key role in the cross-generation maintenance and determination of genotypes. This statement is best understood from a systemic theoretical perspective called organicism.

The roots of organicism can be possibly traced back to Aristotle, but its modern expressions are notably inspired by Kant's analysis of self-organized beings (1790/1987), as well as authors from diverse disciplines during the 19th and 20th century including, for instance, Lamarck (1809), Bernard (1865/1984), Woodger (1929), Bertalanffy (1952), Piaget (1967), Maturana and Varela (1980), Oyama (1985); Rosen (1991), Kauffman (2000) and Walsh (2010). The recent trend towards a more organicist perspective in biology takes place in the context of an increasingly critical attitude vis-à-vis genocentrism (see for instance Gilbert and Sarkar, 2000; Noble, 2008; Walsh, 2015). In spite of their specificities, organicist accounts share some general tenets, which question in particular the unidirectional determination – typically supported by mechanistic and reductionist accounts – between the parts and the whole of an organism. From an organicist perspective, biological systems are *organized* ones, which means that they are composed of differentiated functional parts that depend on each other for their production and maintenance through time (Montévil and Mossio, 2015). In Kant's words, parts of the organism are causes and effects of each other. The authors of this paper have themselves participated in the contemporary organicist trend (Mossio et al., 2016; Soto et al., 2016; Mossio and Pontarotti, 2019), by contributing in particular to the elaboration of a theory of biological autonomy (Moreno and Mossio, 2015).

[5]Strictly speaking, originally the phenotype is a relational notion that supposes a corresponding genotype (Gayon and Petit, 2018, p. 326). From this point of view, talking about the transmission of phenotypes is improper, and presupposes an inflexion of the original Mendelian meaning. A more Mendelian notion is that of "posthumous phenotypes" (Lehmann, 2008; see Pocheville, 2010), that is, phenotypes that extend beyond the generation time.

The mutual dependence among functional parts of the organism seems, at first sight, in straightforward conflict with the idea that the genotype determines the phenotype, but not vice-versa. As a matter of fact, experimental evidence does seem to provide increasing support to the view that the relation between DNA sequences and the whole organism should be understood as one of *mutual determination.* To qualify this claim, we need to distinguish three different senses of mutual determination.

The first, minimal sense of mutual determination is one of *mutual determination of conditions of existence*. That is, the genotype and the phenotype *qua* material structures depend on each other for their maintenance in viable systems[6]. In this respect, one can mention not only the quite obvious fact that DNA is replicated by the cell, but also the now classical studies on DNA repair during ontogenesis: both phenomena show that the conditions of existence of genes are determined by the whole functional organization (Nature Reviews, 2021). This echoes the famous Eigen's paradox, according to which nucleic acids that are long enough require enzymes that are long enough, and vice-versa (see Cornish-Bowden and Cardenas, 2020, for a discussion).

The second sense of mutual determination is one of *mutual specification of causal powers* (i.e. what something does). Namely, not only are the causal powers of phenotypes specified by genotypes but, reciprocally, causal powers of genotypes are, in the absence of any organismic context, underdetermined. For instance, systems biology (Kitano, 2002) has been developed also by recognizing that not only do genes contribute to determining molecular networks but also, and crucially, that molecular networks determine genes' activity (Jaeger and Monk, 2014). The increasing attention to the mutual specification of causal powers has notably been promoted by the difficulty, mentioned above, to elaborate a univocal definition of the gene, and more particularly by the mismatch between the molecular gene and the Mendelian gene. If ascribing a definite function to DNA sequences requires considering the cellular and organismic context where they are located, and with which they interact (or if gene expression is partly stochastic, see Raj and van Oudenaarden, 2008; Kupiec and Sonigo, 2000; Heams, 2014), it follows that the causal powers of the genotype are specified by the phenotype that they contribute to specify.

The third sense of mutual determination is one of *mutual cause-effect relationships* (i.e. genotypes and phenotypes are difference-makers of each other). This questions the received view that DNA sequences are "sealed off from the outside world" (Dawkins, 2006, p. 19). At the scale of gene expression for instance, the DNA sequence is said to specify the proteins' primary sequence (what is usually referred to as its "informational content" (Šustar 2007; Pocheville, 2018; but see Longo et al., 2012), but not the other way around (Crick, 1958; see also Danchin et al., 2019). Yet, processes that contribute to DNA's conditions of existence (notably replication and repair, as mentioned above) are also main sources of spontaneous mutagenesis (Friedberg et al., 2005; Pray, 2008). Hence, not only can differences in DNA sequences make differences in the phenotype, but phenotypic differences (as variations in cellular processes) may also induce genetic differences.

A particular case of causal determination of the genotype by the phenotype occurs when epigenetic processes modify DNA sequences at the time-scale of a single generation, a process that can lead to 'mutational assimilation' (Jablonka and Lamb, 1995, p. 167-9).

[6]Note that conditions of existence concern a different level of explanation than causation. Conditions of existence explain the possibility of existence of a given system, while causation explains how differences make differences on some predicates (Bernard, 1865; Woodward, 2003; Pearl, 2009; see also Stewart, 2004). Thus, the reciprocal determination of conditions of existence does not per se invalidate any putative G-P causal asymmetry.

Mutational assimilation takes place when a defective gene is upregulated to compensate its defective functioning, and when upregulation happens to be mutagenic: in such a regulatory network, upregulation and mutagenicity cease when the organism has found a new, if any, viable state, that may be heritable (Jablonka and Lamb, 1995; Danchin et al., 2019; see also Braun, 2015). Mutational assimilation means that variation, while it remains blind, or "random", at the locus level, may be overall oriented and adaptive at the level of the genome (Pocheville and Danchin, 2017; but see Merlin, 2010)[7]. Note that by taking place at the level of the individual, such reciprocal determination is different from the classical effect of natural selection operating on the long term, at the level of populations and resulting in the differential replication of genes (Hull, 1988).

Since the origins of life, DNA presumably never had an independent existence from biological organization (Forterre et al., 2004). This suggests that the structure, causal power, and functional role of the genotype may have been deeply impacted by the phenotype, and notably by the metabolic activities of organisms as organized systems. This is not to say that, in general, these genotypic and phenotypic elements of the biological organization are on a par: for instance, one may qualify their mutual dependence by taking into account their respective time-scales. Slowly evolving genes may constrain the amino-acids sequences available to organizations at the ontogenetic scale, while organizations may also constrain gene expression and possible mutation rate at various time-scales. This opens an avenue for a more qualified, multi-scale approach of mutual determination in biology (Pocheville, 2019).

4. Implications and objections

The preceding analysis showed that the three pillars underlying the G-P distinction – the distinctions between non-observable and observable, between transmissible and non-transmissible, and between causal and epiphenomenal elements – have limited validity to segregate the components of an organism into two distinct theoretical categories. Not only did the distinction between non-observable and observable elements vanish with the molecular materialization of the gene (be it in terms of DNA sequences or larger structures including notably epigenetic factors), but also, and more importantly, the distinctions between transmissible and non-transmissible elements, as well as between causal and non-causal elements are now put under pressure.

As we discussed, there is increasing evidence that many parts of the phenotype can be directly transmitted, and there are various senses in which the phenotype (or phenotypic differences) can be pertinently said to determine the genotype (or genotypic differences), at various temporal scales. We conclude, hence, that the distinction between the genotype and the phenotype applies (in conformity to the second and third pillars, leaving aside observability) to special rather than general biological situations, although such situations are of central importance for biological knowledge.

Such a conclusion raises the question whether the G-P distinction can keep playing the same structuring theoretical role that it used to play in shaping our understanding of biological phenomena. In our opinion, the reduced validity of the G-P distinction is a sufficient reason for letting it go, and for moving toward a more nuanced and continuist account, in which the relations between the genotype and the phenotype would be replaced by causal relations

[7]Mutational assimilation, which refers to the fact that phenotypes can induce a specific kind of variation in the genotype (*qua* DNA sequence) at the level of the individual, is different from genetic assimilation (*sensu* Waddington), which occurs at the level of the population (Pigliucci et al., 2006).

between comparatively more stable and less stable parts (or 'organizers', to inflect Waddington's (1939 [2016]) term) constituting an organized system. The account would specify - in a system characterized by massive and widespread relations of reciprocal determination - how and to what extent more stable parts *tend* to be more significantly involved in cross-generation transmission than less stable parts, and how and to what extent the former *tend* to unidirectionally determine the latter.[8]

We notably submit that the pervasiveness of extended heredity and reciprocal determination calls for the adoption of an *organizational* account of heredity, whose main principles have been outlined elsewhere (Pontarotti, 2015; Mossio and Pontarotti, 2019). Biological heredity, in this account, refers to the cross-generation *conservation* of an organization of mutually dependent functional elements, which are theoretically characterized as constraints (Mossio and Pontarotti, 2019). Functional constraints can be performed by multifarious elements, including DNA, epigenetic marks, organs, symbiotic microorganisms and socially acquired behaviors. An organizational account aims hence at explaining heredity, understood in an extended way, by putting on center stage the organized system as a whole, endowed with distinctive capacities of self-determination, within and across generations. In this context, the complex relations between molecular genes (DNA portions) and all other traits would have to be reassessed. Characterizing heredity as the cross-generation conservation of functions is compatible with a differential interpretation of determination. Indeed, elements inherited across generations can be interpreted as difference makers as soon as their function in a given organism is compared to the function that they perform when they vary, be it in the same organism in different situations, or in other organisms or species. We actually hold that heredity as the "transmission of variation", cannot be severed from a more general understanding of heredity as conservation (Mossio and Pontarotti, 2019).

At this point, one may reply that the G-P distinction, although weakened, is still widely employed in biological practice. It still allows biologists to do science, to settle experiments, to interpret results, and to communicate among colleagues. At the very least, the distinction is a useful pragmatic one, a convenient linguistic habit acquired by working biologists during their training, and present in all classical textbooks (e.g. Urry et al., 2016, p. 274). More fundamentally, the G-P distinction could still deserve being part of biologists' conceptual toolkit or even, as philosophers would express it, of their scientific "paradigm" (*sensu* disciplinary matrix, see Kuhn, 1970). Therefore, it would not need to be abandoned, but rather reinterpreted within an original theoretical framework in which it would conserve an explanatory role. After all, the concept of gene has been conserved in biological language although its conceptual content has been put under heavy pressure by the advances of biological science.

The objection is sensible, insofar as acknowledging the reduced validity of the G-P distinction does not necessarily lead to its abandon. Yet, we do think that history matters, and that scientists and philosophers cannot easily sever key terms from their older significations. The G-P distinction is intimately related to a specific theoretical framework with its distinctive assumptions, and G-P talk comes with the risk of irresistibly retrieving these assumptions, and putting them at work again, more or less explicitly. One example of such

[8] As a reviewer noticed, a different strategy would be to take a step back from a causal theory of inheritance and espouse statistical concepts such as those of heritable and non-heritable variation, as dissected by ANOVA in quantitative genetics (e.g. Danchin and Wagner, 2010). Although not unrelated to underlying causal theories of inheritance, such statistical concepts do not map straightforwardly to causal concepts (as genotype and phenotype are), and a proper discussion of such intricacies would deserve a paper of its own. We note that the extreme sensitivity of ANOVA to frequency distributions of variables brings such a statistical approach closer to a description of contingent situations than to a theory of biological variation (Lewontin, 1974).

historical inertia can be found in the case of the "missing heritability" (Maher, 2008). Missing heritability refers to the fact that genome-wide association studies revealed that genetic variants explain a surprisingly small amount of variance in common traits. While genetic explanations of missing heritability are available, another kind of explanation is that the identification of the genotype with the DNA sequence, inherited from molecular biology, led biologists to overlook the putative role of epigenetic factors in inheritance (see Slatkin, 2009; Trerotola et al., 2015). More generally, as we discussed, the molecular and Mendelian legacies of the G-P distinction might induce biologists to neglect situating DNA sequences within a larger biological organization.

Science is an evolving intellectual process, and conceptual toolkits need not be eternally efficient. As a result, we do bet that a fruitful epistemological move would be to go beyond the G-P distinction.

5. Conclusion

We examined the conceptual structure of the distinction between the genotype and the phenotype as it was formulated in the specific context of Mendelian genetics. We highlighted that the G-P distinction was grounded on three pillars: the distinction between non-observable factors and observable traits, the distinction between transmissible factors and non-transmissible traits, and the distinction between causal factors and resulting traits.

We argued that subsequent advances in biology – molecular biology, extended heredity, systemic-organicist perspectives – question the general validity of these three pillars (and therefore of the GP distinction), even in the current interpretation of the genotype as DNA sequence. As a result, while the G-P distinction is still relevant in specific situations – such as monogenic diseases –, such a bipartite grid to understand biological phenomena appears to be limited, in particular before the increasing evidence of the transmissibility of phenotypes (and their causal role in heredity) and the mutual determination between parts in biological systems.

Therefore, we pleaded for letting the G-P distinction go, to avoid such a history laden worldview and start afresh. This is our own bet on the question, and readers might have a different sense of the weight of history in science. But whatever the choice on the maintenance of the G-P distinction, biology is now in need of an original framework, that would be more adequate than Mendelian genetics to think about heredity, development and evolution. We suggested that new and relevant explanatory tools could be elaborated from within an organicist, and more specifically an organizational perspective. Its full-fledged elaboration is a stimulating challenge for the future.

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