

**THE ‘MISSING HERITABILITY’ OF COMMON DISORDERS:
SHOULD HEALTH RESEARCHERS CARE?**

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This article critiques the “missing heritability” position, which calls for greater efforts and funding to identify the genetic architecture of common disorders, even if this endeavor has yet to translate into tangible prevention, diagnosis, or treatment interventions. Supporters of the position contend that genetic variants “for” common disorders, which they argue must exist based on heritability estimates (hence their “missing heritability” position), have not been found because the current state of science and technology is not adequate to the task, yet they insist that this search warrants significant societal investments. We argue, instead, that these variants have not been found because they do not exist. The thrust of the problem with the “missing heritability” position, we propose, lies in its proponents’ use of faulty concepts and research methods, including reliance on twin studies, plagued with environmental confounds; on the concept of heritability, a breeding statistic and not a measure of the importance of genetic influences on phenotypes; and on the belief that genetic variations are relevant to understanding, preventing, or treating common disorders, a belief that we argue is false. We elaborate on these problems, discuss their public health implications, and suggest future directions for a critical analysis of human genetics.

Among scientific articles there are [...] not a few wherein the logic and mathematics are faultless but which are [...] worthless, because the assumptions and hypothesis upon which the faultless logic and mathematics rest do not correspond with actuality.

—Wilhelm Ostwald, 1933 (1)

The doctrine that we are the product of our DNA leads to the fantasy that by manipulating [it] we could avoid or cure all disease and even escape eventual death. That is indeed a fantasy. All flesh is mortal.

—Richard Lewontin, 2009 (2)

NOT IN OUR GENES

The belief that differences among humans are rooted in differences in their “natures” goes back to antiquity. Thus, in *The Republic*, Plato asserted that individuals’ place in the social order (i.e., whether they were meant to be artisans, soldiers, or philosopher-kings) depended on their “essences” being bronze, silver, or gold (3). It was not until the late 19th century, with Francis Galton’s work on the “natural” superior intelligence of the British upper classes, that the belief in the overriding power of nature took the form of a plausible scientific hypothesis. At the time, however, the technology to search for the physical substratum of this power—the so-called “genetic basis” of phenotypes¹—was lacking. It was still lacking in the early 20th century, even if the concept of a “gene,” proposed as this substratum, was gaining currency among scientists.

In the early 1950s, the birth of the discipline of molecular biology, marked by the identification of DNA as the substratum of genetic inheritance, and, more recently, the completion of the sequencing of the human genome, gave renewed legitimacy to hereditarian theories of human nature, human behavior, and human disease, which had fallen in disrepute following the discoveries of Nazi atrocities. Yet over the last few decades, hereditarianism has taken on a new guise. No longer is the “nature-nurture debate” one over mutually exclusive categories—everyone agrees that *both* genes and environments cause phenotypes—but rather over *how much* genes contribute to a range of traits, from longevity, to diabetes, to depression (4). Thus, “genetic determinism” is defined based on the *degree* to which traits are attributed to a genetic basis (5). At the same time, a cursory look at both expert and popular publications will lead all but extreme skeptics to believe that this basis has been identified and that it can be isolated from its “environmental” component, quantified, and “targeted” with “personalized interventions” (4).

Nevertheless, by the year 2000, the vision of an all-powerful human genetic science was facing, in the words of renowned geneticist Neil Risch, “a critical juncture” because the methods used to identify the genes “underlying rare mendelian syndromes [were] failing to find the numerous genes causing more

¹ The basic distinction in genetics is that between *genotype*, the material substratum of genetic inheritance, and *phenotype*, any structural, functional, or behavioral trait of an organism. Phenotypes result from the non-additive “mix” of an organism’s genes, a range and sequence of environmental exposures, and developmental random noise (random chemical reactions in the inter-cellular and intra-cellular mediums).

common, familial, non-mendelian diseases” (6), genes whose existence is presumably revealed by heritability measures. Yet hope was placed in the Human Genome Project, then nearing completion, which would provide, according to Risch, “new opportunities . . . for unraveling the complex genetic basis of non-mendelian disorders based on large-scale genome-wide association studies [GWAS].”²

Yet, a decade into the completion of the first working draft of the human genome, the discipline finds itself at an even more critical juncture, after a generation of psychiatric genetic researchers, including Risch, have tried, yet failed, to identify the genes they believe underlie, “at least in part,” major psychiatric disorders (7–9), even though in the 1980s most of them expected the “rapid” detection of such genes (10, 11). Meanwhile, their biomedical counterparts celebrate “findings”—associations between gene variants and common conditions—that “explain,” statistically, a tiny fraction of the genetic variance, add nothing to the predictive power of traditional clinical markers, and make no difference to disease prevention, onset, or treatment (12, 13), that is, clinical, public health, or other interventions already known to be useful (4).

The sober track record notwithstanding, a growing number of genetic researchers are now reassuring us that the heritability of common and complex conditions—a coefficient they assume indicates the presence of gene variants “influencing” those conditions—must exist and is simply “missing.” The problem, we are told, is that these “disease genes” have found very good hiding places and, moreover, are not what we thought they were (i.e., not just a few, very common, and of small effect size, but rather *rare, many*, and of *potentially large effect size*) (14–18). Researchers also assure us that the prize is around the corner—we merely need newer technologies, better research designs, or larger samples—because years of observing ethnic and familial aggregation of these disorders, or of estimating heritability via twin or adoption studies, have provided “clear evidence” for the existence of these genes (16, 18–20).

But what if the very enterprise of attempting to understand which variations in the human genome produce which variations in the overwhelming majority of medical, psychiatric, and behavioral phenotypes led nowhere? What if *current* knowledge about gene variations *already* indicated that gene variants

² Genome-wide association studies (GWAS), used extensively since 2005, involve rapidly scanning markers across the genomes of many people to find common genetic variants statistically associated with particular diseases or traits. GWAS focus on *common* gene variants, that is, those found in 5 percent or more of the population. The dominant view in human genetics and the rationale for GWAS has been that there is an identifiable genetic architecture of common variants underlying common disorders—the “common disease, common variant hypothesis.” The failure to identify these variants has led investigators to claim that it is “rare” variants—defined as variants found in less than 0.5 percent of the population—that may be responsible for common diseases and that will be “found” with larger samples, better designs, or new technologies.

are irrelevant to mental and physical health and to social behavior generally? What if expressions such as gene variants “influence,” “are implicated in,” or “contribute to,” among many others, were either trivially true or meaningless? What if, in sum, the attention to genetic variations were merely a distraction from the social determinants well-known to determine, on average, who gets sick or remains healthy or to influence the wide range of human behaviors, whatever an individual’s genetic makeup?

In this article, we focus on the so-called “missing heritability” of common clinical diseases and mental health conditions (hereafter “common disorders”). By “missing heritability,” we allude to the position put forward by leading genetic researchers (14, 21) in light of the failure to discover most of the gene variants that they believe cause, to varying degrees, disorders that are common in clinical or mental health practice; pose important societal challenges, such as great suffering or significant health care costs; and are characterized by a frequency of about one in every 1,000 individuals (22). The 2009 *Nature* publication of “Finding the Missing Heritability of Complex Diseases” has served as the primary reference point for the position (14). The authors argued that “missing heritability” was the “dark matter” of current genetic studies, meaning that “we” (i.e., *they*) are sure it exists and can detect its influence, but simply cannot yet see it (14). We argue, instead, that there are very good reasons to believe gene variations are at best irrelevant to common disorders and at worst a distraction from the social and political roots of major public health problems generally and of their unequal distribution in particular.

Our critique does not apply to “single gene” conditions like Marfan syndrome, Huntington’s disease, or phenylketonuria. In these cases, we wholeheartedly agree that medical genetics has played a role, even if all too often, treatments, if they do exist, are environmental (e.g., a special diet). In such cases, identifying gene variants causally related to the condition at hand is, and has been, often possible and even worthwhile. Nor do we dispute the importance of genetic knowledge to issues such as reconstructing human ancestry or understanding processes of development and molecular interaction. However, it is not these, but the “promise” of unprecedented benefits for human health that has been the overwhelming justification for the immensely expensive effort of sequencing the human genome (2), on the premise that the enterprise will “uncover the hereditary factors in virtually every disease” and thus enhance the prevention, diagnosis, or treatment of common disorders (23).

As we shall argue, the thrust of the problem of the “missing heritability” hypothesis lies in its proponents’ reliance on faulty concepts and research methods, summarized as follows:

1. The hypothesis is based mainly on twin studies and, to a lesser degree, family and adoption studies. However, obvious and invalidating environmental confounds are usually denied, dismissed, or outright ignored.

2. The hypothesis is based on the too often misunderstood and misused concept of heritability, a breeding statistic and *not* a measure of the importance of genetic influences to phenotypes.
3. The hypothesis is based on the belief that genetic variations must be identified to better understand, treat, or prevent common disorders, in turn based on the belief that all major variations in phenotypes (e.g., differences in health status) are caused by variations in genotypes. However, for disorders defined as “common” in this article, gene variations are irrelevant.

In the following sections, we elaborate on these three problems, discuss their public health implications, and suggest future directions for a critical analysis of human genetics.

TWIN STUDIES: SCIENCE OR PSEUDOSCIENCE?

Most publications in the field of molecular genetics concerning common disorders begin by stating that the genetic basis of the disorder has been firmly established on the basis of family, twin, and adoption studies, thus providing the rationale for their investigations (19, 24–28). However, family studies are generally recognized as unable to disentangle the relative weights of genetic and environmental factors. Adoption studies are problematic, and relatively few have been performed. Accordingly, studies of reared-together twins constitute the main evidence cited in support of a genetic basis for common disorders (29, 30).³

The chief research method using twins is the *twin method*, which compares the trait resemblance—measured with correlations or concordance rates—of reared-together, monozygotic (MZ) twin pairs (also known as identical twins, who share 100% genetic similarity) with the trait resemblance of reared-together, same-sex dizygotic (DZ) twin pairs (also known as fraternal twins, who

³ Supporters of the twin method have proposed studies of twins reared apart to overcome methodological problems of twins-reared-together studies (94, 95), yet these studies have their own set of problems, biases, and environmental confounds (30, 34, 96). Adoption studies also have their own set of problems, which even leading behavioral genetic researchers have discussed and acknowledged (35). A carefully designed 1998 Colorado Adoption Project study of personality found that the mean personality scale correlation between birth parents and their adopted-away biological offspring—a relationship they considered “the most powerful adoption design for estimating genetic influence”—was *zero* (97). Thus, on the basis of this study, we could conclude that genetic factors *play no role, at least in personality formation*. These negative findings are rarely mentioned by psychiatric geneticists, behavioral geneticists, the authors of scholarly reviews, journalists, or the authors of books appearing since 1998 that popularize genetic research. If these findings are mentioned, they are quickly dismissed (94, 98, 99).

average a 50% genetic similarity). Researchers count twin pairs as *concordant* when both members are diagnosed with the same disorder and *discordant* when they diagnose only one member of the pair. Based on the assumption that the childhood and adult environments of MZ and DZ pairs are equal, known as the *equal environment assumption* (EEA) (or *relevantly* equal, i.e., trait-relevant EEA), twin researchers conclude that genetic factors explain the usual finding that MZ pairs are significantly more concordant than DZ pairs (29).

Yet it is precisely in the assumption that the environments shared by MZ and DZ twins are equal that the *first and most critical* problem with the twin method lies, because a wealth of research has established that these environments are anything but equal, that is, that the EEA is false (31–34). Indeed, most contemporary twin and molecular genetic researchers themselves acknowledge that MZ pairs experience much more similar environments than DZ pairs (35–38). Factors contributing to these similarities include the substantially different uterine environment and development of MZ and DZ twins, both of which have clinically significant effects on childhood and adult health (39), and the much closer emotional bond experienced by MZ twins, which often leads to “identity confusion” (38, 40, 41). However, to the best of our knowledge, these findings are rarely discussed in publications addressing the genetics of common disorders, and when they are, they are dismissed or overridden by assertions about the “compelling” evidence that diabetes, autism, or other common disorders have a “substantial genetic component” (19).

Interestingly, twin researchers’ ultimate defense of the EEA and the twin method *comes down to a single argument*, which admits up-front that MZ pairs *do* experience more similar environments than DZ pairs, yet immediately qualifies this assertion with the proposal that those environmental similarities are “caused” by MZ pairs themselves (who are genetically more similar to each other than DZ pairs), a reasoning that we have called “twins create their own environment” theory (41).

Kenneth Kendler was perhaps the first twin researcher to put forward a detailed theoretical and empirical justification of the EEA via the detour of the “twins create their own environment” position, 60 years after the twin method was developed (42). In 1983, Kendler wrote that “the available evidence suggests that the similarity of the social environment of monozygotic twins is the result of the behavioral similarity of the twins” (42), which he attributed to the twins’ presumed behavioral genes, thus concluding that the EEA and the twin method are valid because “the similar phenotypes in monozygotic twins are caused by their genetic similarity” (42). Similarly, Zerbin-Rudin wrote that “MZ twins create a similar environment through their greater [genetic] similarity,” which explains the “large difference between the concordance figures for MZ and DZ twins” that “cannot be explained exclusively by the more similar

environments of MZ twins.” “Thus,” concluded the author, “in a roundabout way, we still come back to the importance of heredity” (43).

To note, neither Zerbin-Rüdin nor Kendler noticed the circularity of the “roundabout” method they and other twin researchers have used to argue that MZ–DZ correlational or concordance rate differences are caused by genetic factors. However, circular reasoning provides no knowledge other than that which we already have, or believe we have. An example of such reasoning is the case of the instinct theorist who, when asked why all the sheep in an open field clustered together, replied, “Because they have a gregarious instinct.” When he was asked how he knew sheep had such an instinct, he replied, “It’s obvious. Just look at them all clustered together” (44). Instances of circular reasoning published in peer-reviewed journals over decades are too numerous to repeat, but suffice it to say they are impossible to miss. A recent, typical example is that of twin researchers Sturgis and colleagues, who write, “MZ environments are more similar than DZ environments . . . *because of the initial difference in genetic predispositions*” (italics in original) (45).

The argument that “twins create their own environment” presents further problems: even if twins *did* create more similar environments for themselves because of their greater genetic similarity, MZ pairs could still show much higher concordance for a host of common disorders than DZ pairs for purely environmental reasons. Let us assume, for instance, that we measure the concordance rates of skin cancer among MZ and DZ twins and find them to be higher among the former. We know that exposure to ultraviolet light causes skin cancer (46), so a reasonable explanation for our finding would be that MZ twins spend more time together—including sunbathing—than DZ twins, for a variety of psychological or sociological reasons, hence the greater concordance of cancer among them.

Interestingly, confronted with this type of evidence, twin researchers assert that twins spend more time together (including sunbathing) for “genetic reasons” (a “sunbathing gene”?) and thus conclude that differences between concordance rates of MZ and DZ twins provide “compelling evidence” that whatever the observed trait, it is ultimately “caused” by genetics and not by contingent environmental exposures (41). Behavioral geneticists Plomin and Asbury do just that. They have labeled what they believe to be the fact of genes “creating” their own environments—for instance, children’s “genetically driven” behaviors influencing parental behavior toward the child—“the nature of nurture” (20).

Indeed, the “twins create their own environment” theory proposes a strange family environment: genetically-programmed children meeting their ever-so-flexible parents, who can toss aside their own “genetic blueprints” to adjust their behavior to their children’s “genetically determined” behaviors and personalities (32).

HERITABILITY: WHAT IT IS AND WHAT IT IS NOT

Let us move on to the *second critical problem* of the missing heritability position: the misunderstood and misused concept of heritability itself. The missing heritability position presupposes that heritability is a useful concept that measures the significance of genetic influences. But if the concept itself is misused, this would undermine a position that claims that the concept is “missing”—it would make the position either false or unintelligible. Elsewhere, we have elaborated on the concept of heritability (47). For our current purpose, suffice it to reiterate that a key problem is how to interpret heritability claims. By way of an example, let us take Katoh and colleagues’ claim that their computation of the heritability of fasting insulin levels (a marker of type 2 diabetes, hereafter “diabetes”) is 43 percent (48).

One way of interpreting the statement would be to say that 43 percent of Katoh’s *identified cases* of diabetes are fully explained by genetic causes, while 57 percent of identified cases are explained by environmental causes. This interpretation, however, cannot be correct, because researchers appear to agree universally that diabetes results from *interactions* between “several altered genes” (49) and a range of environmental factors, not in *some* but in *all* individuals who develop the disease (50–52). Virtually all of them agree that lifestyles, an environmental factor, play a critical role in the etiology of diabetes and give no hint that their recommendations of adopting healthy lifestyles to prevent diabetes apply to some (genetically predisposed) individuals but not to others. So, again, how are we to interpret Katoh and colleagues’ heritability claims?

Should we take it to mean that, for a given individual in their heritability study (or perhaps for the *average* subject), 43 percent of their diabetes is caused by genes and 57 percent by diabetes-relevant environments—what they have eaten, exercised, and so forth? This reading *seems* to make sense and indeed presupposes that *both* genes and environment play a causal role in diabetes (or any other common disorder). Yet it then goes on to assume that the relative weights of both can be quantified. Now, this assumption is not obviously false. When two factors jointly cause a given effect, one can often ask how much each factor contributes. For example, if a massive charged body is undergoing acceleration, it makes sense to ask how much of the acceleration is due to its mass (effects of the law of gravity) and how much is due to electrical charges (effects of Coulomb’s law) (53).

But if we can say of a study subject that 43 percent of her diabetes is caused by her genes and 57 percent by her environments, we must be able to say something similar of any of her phenotypic traits, for instance, her height. The same subject’s height also is caused by her genes and her exposure to relevant environments—nutrition, childhood diseases, and so forth. But from acknowledging the contribution of genes and environments to height, does it follow that we can meaningfully ask how much of this subject’s total height comes from her genes and how much from her environment? Would it make sense to claim that

if this person is five feet tall, 43 percent (roughly two feet) comes from her genes and 57 percent (roughly three feet) from the environments contributing to this height? Or vice versa?

Evidently, there is a problem with attributing one percentage of anyone's height, or diabetes, or depression, to genes and another to environmental factors. The problem lies not in *which* numbers are attributed, but *in the very fact of attributing a number, any number*. Such an attribution makes no sense: it does not permit of truth or falsity. The same is true with any other complex human phenotype. But why is this so?

The following example, proposed by population geneticist Richard Lewontin, shows why heritability measures fail to answer the question of *how much* genes contribute to phenotypes, that is, to illuminate the nature-nurture question. If two bricklayers build a wall, one can calculate how much of the wall each worker built by counting the number of bricks each one added. In contrast, if two workers build a wall, one by laying bricks and the other by mixing mortar, it would not make sense to quantify their relative contributions by measuring the volumes of bricks laid and mortar mixed (54). The two workers' contributions are not independent of each other. Therefore, there are no common units with which to measure how much of the wall each worker built (i.e., caused).

Now, one could decide that what matters is the number of hours each worker put in, or one could assign values to bricklaying or mortar mixing to estimate compensation. Yet this number would not measure *how much* of the wall each worker helped bring into being, but rather reflect our subjective judgment about the relative worth of different tasks.

Likewise, genes and environments do not build phenotypes independently, so there is no common unit of measurement that enables us to say that in one individual, genes "caused" x percent of some trait, while the environment caused y percent. The *appearance* of sense is a rhetorical illusion. In the acceleration of a massive particle, gravitation and electrical forces do operate independently of one another. Units of force do provide a common currency for stating their relative contributions. In contrast, phenotypes are the non-additive product of genes, a range and sequence of environments, and developmental random noise. The interdependence of these "ingredients" makes the task of quantifying their relative contributions meaningless (55).

This is why the claim that 43 percent of someone's diabetes (or height) is caused by genes and 57 percent by relevant environments in the course of its development is nonsense—literally. Nor can this claim be taken to mean that for the average member of the population studied, the contribution of genes to diabetes is 43 percent. *This is because heritability is an attribute, not of the traits of individuals but of traits in a population*. Indeed, Katoh and colleagues themselves write that "heritability is a population-specific characteristic that has *no interpretation on the level of the individual or the family*" (emphasis added) (48). Still the question remains: what exactly does a 43 percent heritability measure?

As defined by Jay Lush in the 1940s, heritability is “the fraction of the observed or phenotypic variance [...] caused by differences between the [...] genotypes of the individuals” (56). Thus, heritability quantifies the extent to which variations in the genomes of a given population (with a certain genetic background and distribution of genotypes) under a given range and sequence of environmental exposures relevant to the development of the trait at hand explain, statistically, variations in the trait. It is, therefore, correct to claim that the heritability of diabetes in a given sample is 43 percent. Yet change the size of the sample, or the type or relative composition of genotypes in the population, and the estimate will change. Change the range or sequence of environments under which those genotypes were studied, and the estimate will change, even when the diabetes status of each individual has not changed. As Lush specified, change any of the variances and the heritability of the trait will change, because heritability is an estimate of the relative contribution of genotypic variance to total phenotypic variance, *not an analysis of the causes of the trait* (54).

So the problem with heritability, whether of diabetes or any other trait, is that it is not an estimate of what everyone would like it to be, an analysis of biological functional relationships, a measure of how much of a person’s diabetes is caused by her genes. Rather, it is *a local, spatiotemporal analysis of variances* (54), an estimation of how much of the genetic variation in a specific population of a specific genetic composition and distribution exposed to a specific range and sequence of environments explains, statistically, that population’s phenotypic variability.

For this reason, heritability coefficients have a place in agriculture and farming, where environments can be manipulated to breed the desired specimens, yet have no place among human populations. As behavior geneticist Douglas Wahlsten wrote, “The only practical application of a heritability coefficient is to predict the results of a program of selective breeding” (57). Thus, heritability measures *cannot* be useful to health researchers, who do not seek to weed out “bad” genotypes and select “good” ones to produce “desired” traits in the given or current environments, but rather need knowledge that can help improve the health of the patient population they have, inform interventions effective for the greatest number of human genotypes, shed light on which environments will allow population health to flourish, and advocate for them if at all possible—all illuminated by the wealth of knowledge already available about common disorders.

IS HERITABILITY A MEASURE OF THE IMPORTANCE OF GENETIC INFLUENCES TO A TRAIT?

Do heritability coefficients measure the importance of heredity—of the genes bequeathed to us by our parents—to how we look, function, or behave? The

short answer is no. This is because it follows, from Lush’s widely accepted concept of heritability as a ratio of variances, that it is perfectly possible, under certain environments, for a completely environmental trait to have a heritability of 100 percent or for a completely inherited trait to have a heritability of zero. As psychological researcher Lerner pointed out, in a society where eligibility for government office was reserved exclusively to men, the heritability of “being eligible for government office,” arguably an “environmental” trait, would be 100 percent, because if one divided the population between women (with 0% chance of being eligible) and men (with greater than a 0% chance), all one would need to know to make sound predictions would be whether an individual possessed an XX pair of sex chromosomes or an XY pair (58). In other words, the heritability of “being eligible for office” would compute all the phenotypic variability as explained (statistically) by genetic variability. It is also clear that no “genetic knowledge” would be necessary to change what many would consider an unjust state of affairs.

Conversely, a fully inherited trait, such as having five fingers, which clearly does not vary with variations in nutritional states, childhood diseases, sun exposure, cultural practices, place of birth, and so forth, and is caused by our human genome *somehow*, can have a heritability of zero if measured in a population in which, for instance, some individuals worked with machines that could sever their fingers and some did not. Generally, none of the variation we might find *in the trait in that population* would be caused by genetic differences but by environmental ones, unless one postulated gene variants that “predisposed” certain individuals to work with such machines (a type of “genes create their own environments” theory).

The following example, provided by developmental psychologist David Moore, further illustrates the fallacy of claiming that heritability measures the importance of genetic inheritance (59). Snowflake formation requires both high relative humidity and a temperature below 32 degrees Fahrenheit. Because temperatures at the North and South Poles are constant—always below freezing—while relative humidity varies, all snowflake variation at the North and South Poles can be explained by differences in relative humidity. In other words, the snowflake relative humidity “heritability” in this case is 100 percent.

Conversely, snowfall variation in tropical countries, where humidity is always high and snow falls at the highest mountaintops, is explained by temperature variation alone. That is, the snowflake relative humidity “heritability” is now 0 percent, whereas its relative temperature “heritability” is 100 percent. This example reflects the fact that in each situation, a key variable has been held constant, and the percentages tell us nothing about the relative “importance” of humidity or temperature to snowflake formation. The same holds true for the relative importance of genes or environment to common disorders.

IS KNOWLEDGE OF GENE VARIATIONS NECESSARY
TO EFFECTIVELY INTERVENE IN
COMMON DISORDERS?

As noted in the introduction, the *third and last problem* of the missing heritability hypothesis is that it assumes knowledge about gene variations will necessarily improve the prediction, diagnosis, prevention, or treatment of common disorders. But will it? The concept of reaction norm, a property of the genotype known by geneticists for close to a century and representing the relationship among genotypes, environments, and phenotypes (55), helps answer this question.

When, in elaborating the reaction norm of a given genotype, “environment” is plotted on the x axis and “phenotype” on the y axis, it becomes apparent that *phenotypes vary as environments vary*. With the exception of naturally-occurring or lab-produced mutants, the relationship between genotypes and phenotypes varies as the range and sequences of environmental exposures vary. For example, a plant with a genotype A may be taller than one with a genotype B at sea level, shorter than plant B at 3,000 meters, and equal to B at 1,400 meters. This relationship is illustrated by an experiment in which seven specimens from a California herb of the same genus and different genotype were collected from the wild, and three cuttings were obtained from each (55). Cuttings from each genetically identical specimen were planted at different altitudes. The genotype that grew the tallest at sea level was not the tallest at 1,400 or at 3,050 meters. Similarly, the tallest at 3,050 meters was not the tallest at the other levels. In fact, no single genotype was consistently taller or shorter than others over the range of environments examined. Indeed, knowledge of the genotype did not allow researchers to predict which plant would be taller or shorter. In fact, the very question “Which plant (genotype) is the tallest?” made no sense because different cuttings were taller or shorter *depending on the environments in which they grew*. In certain environments, their height was the same, which is equivalent to saying that in those environments, *their gene differences made no difference*.

It follows from this experiment that expressions such as “a genetic tendency to X” are biologically empty unless all relevant environments are specified, which requires that we know what those environments are. “Tendencies” do not occur in a vacuum: a “gene for tallness” at sea level may become one for shortness at 3,050 meters and may be irrelevant to height differences at 1,400 meters. So it is incorrect to conclude, as diabetes researcher Barroso does, that differences in diabetes prevalence between “minority ethnic groups living in the US and in the UK” when compared to “comingled subjects of European descent” support “the idea of genetic factors contributing to disease predisposition” (19). The researcher has merely *assumed*, while providing no evidence, that the environmental exposures of “minority ethnic groups” and “comingled subjects of European descent” are equal.

Most importantly, it also follows that if the goal is to improve the public's health, there are years, if not centuries, of evidence demonstrating which *environments are most advantageous to the development of the healthiest human phenotype, regardless of genetic makeup*: these are environments in which individuals are assured basic resources for health and well-being from conception on. Further, real medical breakthroughs, like the discovery of insulin or the polio vaccine, did not require an iota of "genetic knowledge" about affected individuals, yet they have saved millions from disability or death for nearly a century, provided the resource was made available. Resource availability, of course, is not a problem of genetics, but of economic and public health policy.

DO OUR GENES MAKE A DIFFERENCE?

At this point, skeptical readers may still think our claim that gene variants are irrelevant to common diseases cannot possibly be true. After all, as science blogger Mary Carmichael reasoned in her post *DNA, Denial and the Rise of 'Environmental Determinism,'* if a child's nose resembles her parent's, it cannot be because she grew up in the same house (i.e., for environmental reasons). If genes make a difference to whether children's noses resemble their parents', she concluded, how could any reasonable person doubt that they make at least *some* difference to who gets sick, and of what (60)?

That nose resemblances cannot be attributed to sharing a household with our parents is no doubt correct. But does it follow that if we share our parents' language, it is due to our genes? It obviously does not. But how do we know? We know because we understand the developmental history of language acquisition, enough at least to know that what matters in this case is early exposure to a language, regardless of whether individuals share genes. So we can confidently conclude that in this case, environmental factors alone make the difference (i.e., cause), not in a child's mastery of a human language per se, but in her mastery of a specific language, and that gene variants are irrelevant.

Of course, by rejecting genetic explanations for language acquisition, we do not mean that genes do not cause it in any way. After all, for someone's pet dog, no amount of growing up in the same environment would do the job of "causing" a dog to master a human language. In *some* sense, this would be for "genetic reasons"—mastering a human language requires human, not dog, genes. So when it comes to explaining differences in language acquisition between children and puppies—a difference between rather than within species—genes are indeed one, albeit not the only, difference-maker (even if the specific difference-making genes causing humans to master any human language are yet to be identified).

But that is not what supporters of the genes-view of common disorders mean when they assert that some individuals are "genetically predisposed" to such disorders. They do not mean that a human genome is necessary to develop those diseases, but that some individuals have one or more specific gene variants that

cause—that is, are the difference-maker of—their disease states, to some quantifiable degree, when compared to *other* humans. They also mean that those not predisposed would remain free from disease *even under exactly the same spatio-temporal exposures relevant to the developmental history of these disorders*, a *ceteris paribus* clause that is assumed, yet for which evidence is never provided.

Now, if we knew nothing about the developmental history of language, which conclusively shows that gene variants do not explain differences in ability to master one language over another, we might attribute the fact that languages generally run in families to as-yet undiscovered genes. In fact, we could hypothesize that for any complex trait that “runs in families,” whatever may have caused them, one among the thousands of genetic variations that biologically-related individuals surely share—and that increasingly potent technologies and larger samples allow us to identify—might be the gene “for” that trait. Obviously, individuals who bear greater genetic resemblance because of their biological relatedness will bear a host of other resemblances, so their genes will be statistically associated with their traits, whether or not there is any real causal connection. This is why it is generally accepted that familial aggregation cannot disentangle genetic and environmental influences (61).

Yet the fact that a trait runs in families still leads to claims about presumed “genetic influences,” as it did a century ago in the American South, when pellagra was declared to be partly “genetic” *because* it ran in families (62, 63)—incidentally, *poor* families—even if this turned out to be false. Let us note that even if there existed a “genetic predisposition to pellagra,” pellagra was wiped out with the addition of niacin to basic staples, so if the descendants of former sufferers bore anything like their parents’ “genetic predisposition” to it, we will never know (64). We do know, however, that the phenotype “free from pellagra” is invariant (i.e., displays no relevant variations) when the population is properly nourished, in which case individuals’ genes make no difference to their pellagra-free status. Few would argue that we should undertake a search for “pellagra genes” if there were a new outbreak of the disease, rather than ensure everyone receives the right amount and type of food.

Remarkably, however, as new gene variants for “depression upon exposure to child abuse” (65) or “developing emotional problems by age 12 upon exposure to bullying” (66) are “identified,” researchers keep telling us in glowing terms that these findings could lead to public health interventions, such as greater efforts to decrease child abuse or bullying, undoubtedly wholesome pursuits. Yet if we pushed these assertions to their logical conclusions, we should be performing molecular genetic studies to demonstrate the harmful physical and psychological effects of hunger, poverty, war, and so forth, which would actually *promote* these harmful conditions, exactly the opposite of what these researchers claim.

Unfortunately, faced with the mindboggling statistical computations and jargon of genetic studies, uninitiated readers often walk away from these discussions shrugging their shoulders and concluding, quite reasonably, that if their child’s

nose resembles theirs, genes must also influence (i.e., cause) matters of life, health, and death. What’s more (and more troubling), as the mass media reproduce uncritically the views of prominent scientists about the latest genetic “discovery”—ranging from genes “for” committing crimes (67), voting conservative (68), or believing in God (69)—readers often conclude that the contributions of “life, health, and death” genes can be identified, quantified, and targeted with “personalized” strategies and that whoever denies all this must be crazy, ignorant, or an “environmental determinist” (60).

Meanwhile, negative “findings” (i.e., of replicable correlations between “disease genes” and common disorders) continue to be rationalized on the grounds that failures are an expected outcome of investigations into “multifactorial-complex disorders” (70, 71) and that all we need is larger samples, better technologies, or more research money (14, 15, 66, 72). But there exist alternative explanations for the negative “findings” that would lead to radically different courses of action to address major public health problems. One is the extreme resilience of complex phenotypes (e.g., common disorders) to variations in the genome—a phenomenon called “genetic robustness,” which refers to the “constancy of the phenotype in the face of genetic, epistatic (between genes) or epigenetic perturbations” and provides phenotypes a “buffer” against the expression of mutations (73). Another explanation, recognized by genetic researchers themselves, is the “context-dependent” nature of genotypic expression, so while “predicting . . . complex phenotypes in the laboratory can be quite accurate . . . when the same genes and phenotypes are projected into a free-living population, individual prediction entails *too many additional variables*,” so even if one represented “a projected norm of reaction . . . *it is nearly impossible to know how useful such a prediction would be*” (emphasis added) (74).

Translated into plain English, these researchers are conceding that the correspondence between genotype and phenotype is anything but one-to-one; that variations in the genotype will not necessarily result in variations in the phenotype, let alone in “diseased” (or healthy) phenotypes; and that the enterprise of identifying “genes for” complex phenotypes in the real world is like shooting a moving target. Notably, they still find the paucity of “findings” in GWAS “striking” and list as possible explanations for this failure “missing low-frequency” (“rare”) alleles, the genetic heterogeneity of the trait, genotype-environment interaction, “epistasis,” or “inadequate research designs” (75). In all cases, they refuse to consider that a very plausible interpretation of the “striking” (non) finding is that genes “for” common disorders phenotypes have not been found *because they do not exist*. In 2009, Richard Lewontin asked, “Where are the genes?” (2). This question remains equally relevant today.

THE BEST OF ALL POSSIBLE WORLDS?

At this point, we should note that molecular genetic research assumes that the society in which it is undertaken is basically healthy and does not systematically

cause great numbers of people to suffer major physical or psychological distress—if they do, they must have some “genetic predisposition.” But what if “traditional” psychological, public health, or sociological theories are correct in pointing to the family, nutritional, school, neighborhood, or larger environments over the life course, as well as drawing attention to the harmful effects of living in poverty, chronic stress, racism, the oppression of women, and so forth, as playing critical roles—in fact, *the* critical roles—in a person’s potential for physical and mental health, as years, if not centuries, of research into the social and political determinants of health have shown (76–82)?

From this perspective, whatever “genetic predisposition” there might be—assuming the notion were meaningful—would be of little if any interest, and societal resources would be invested in improving social and family conditions, creating free universal health care, promoting equality, eradicating racism and other forms of oppression, guaranteeing full employment and living wages, and so on. If unhealthy family, social, and political arrangements are indeed the factors underlying public health problems, especially health inequalities, then focusing on genetics is a monumental diversion, comparable to focusing on the alleged genetic predisposition of smokers who develop lung cancer—after all, not all smokers develop it—rather than on the mass propaganda and powerful lobbying of the tobacco industry, to divert attention from the carcinogenic effects of tobacco (83, 84). The following example will further clarify this point.

Suppose that in the 19th century the unthinkable had happened—the Confederacy had won the Civil War and maintained itself into the 21st century as an independent country based on black slavery. Let us further suppose that researchers at the University of Alabama announce that they plan to conduct molecular genetic studies so as to pinpoint the genes that predispose black slaves toward malnutrition, depression, psychosis, “drapetomania” (runaway slave disorder), and so on. We are certain that most people outside the modern-day Confederacy, including most molecular genetic researchers in the United States and Europe, would be appalled with this research program: they would assume that being held in slavery cannot fail to cause extreme physical and emotional distress, see such molecular genetic studies as a clear case of using science as a means of social control, and advocate for the abolition of slavery as the only “cure” for these “disorders.”

Similarly, theories of disease that pay only lip service, if anything, to the social determinants of health and urge us instead to “uncover” the “genetic basis” of common disorders are using science as a means of social control to divert attention from the dire living conditions, political disempowerment, and widening inequalities that exist all over the world. These are increasingly common in the United States, which in 2010 registered 49.1 million people in poverty, the largest number ever published (84), and where the wealth gap among ethnic groups has *doubled*—from 10 to one to 20 to one—in *less than five years* (86). So assuming “roughly equal environmental conditions” between “minority ethnic

groups" and "comingled subjects of European descent" (19), or asserting there is a "compelling" need to gain a better understanding of the genome to improve human health (87) is problematic at best.

CONCLUSIONS

We have argued that the three main problems of the "missing heritability" stage of molecular genetic research are (1) a reliance on twin studies, which are unable to disentangle the relative causal contributions of genes and environment; (2) a reliance on heritability statistics, a useless concept in human genetics and not a measure of the "importance" of "genetic inheritance"; and (3) the belief that knowledge of gene variations is critical to better intervene in common disorders, such that its acquisition deserves substantial societal investments.

At this point, let us reiterate that our analysis and conclusions apply exclusively to what we defined as common disorders. Let us also note that there is no contradiction between arguing that the roots of disease are social and acknowledging the reality of human biology. In other words, we are not pitting social *against* biological, or psychological, causes of disease. After all, anything in the world that affects human health (e.g., public policies leading to wars or to poverty) ultimately acts upon bodies or minds, and biology and psychology can provide detailed accounts of the proximal causes of disease. In other words, everyone dies from "cardiac arrest," one way or another, whatever the distal cause of the failure might be (e.g., someone pulling a trigger, a long disease, or merely old age).

Still, we insist that our critique of the search of the genetic basis of common disorders is not triggered, as has been suggested, by the fear of "lay people and incompetent scientists" that it may lead to a repeat of the notorious sterilization programs of the early 20th century or the Nazi atrocities of World War II (11). Even so, we believe the track record of scientific theories of "essential" differences among human beings and "races" provides good reason for concern, and we note that massive programs of sterilization and genocide that drew their legitimacy from these theories took place in the most "civilized" and technologically advanced nations on Earth (88, 89). Rather, we are critiquing the scientific foundations of a research program that we argue may turn out to be a "null field," an area of research "with absolutely no yield of true scientific information" (90). For example, it appears safe to assume that a branch of medical research dedicated to identifying dietary patterns causing Huntington's disease would eventually turn out to be a 'null field.'" As Ioannidis noted, researchers working in such a discipline "are likely to resist accepting that the whole field in which they have spent their careers is a "null field," yet additional evidence, or more importantly, a persistent lack of evidence "may lead eventually to the dismantling of a scientific field" (90), a dismal outcome for those who have built their careers, professional identities, or fortunes around it.

So what can health researchers do, especially those with little or no expertise in genetics? First, because the validity of the twin method is central to the missing heritability hypothesis, they could call for the creation of an independent commission to investigate the validity of twin research and molecular research more generally. The commission would give equal weight to previous and current arguments by twin and molecular genetic researchers and their critics. The commission would include only a minority of twin and molecular genetic researchers and of any individuals with financial conflicts of interest in the matter, for the same reason that a commission investigating whether pesticides harm human health would limit the role of pesticide company executives. The commission also could investigate the resilience of the genetic paradigm, especially in academia and the media, institutions that legitimize this paradigm, today as strongly as ever, even when it is very likely that “the emperor has no clothes” (4).

In the words of Latham and Wilson, the absence of disease genes is “without question a scientific discovery of tremendous significance” (91) and the fact that it is persistently ignored, denied, or dismissed is well worth investigating. It is also critical to investigate how genetic knowledge is produced *to evaluate the science on its own merit*. As sociologist Troy Duster noted when investigating scholarship on crime, social theories of crime built on flawed data, concepts, or methodologies are not reliable, however “social” they might be (92). This is as true for genetics as it is for “softer” disciplines.

Last, we agree with the leading figures of medical, psychiatric, and behavioral genetics and others who write about being “at the dawn of a new era.” But the new era that we envision is one in which it will be recognized that genes for common disorders are either nonexistent or irrelevant and that the attention of the health and social sciences must focus on the familial, sociocultural, and political environments leading to, as Rose put it, the “social and personal distress in advanced industrial societies” (93). At the present time, medicine, psychiatry, and other health-related fields have chosen to locate this distress largely within the genes of individuals and then assign them the status of “diseased.”

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