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THE CONCEPT OF GENETIC DISEASE
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1. Introduction: Genetic Diseases

It is generally accepted that there are around 10,000 human diseases associated with variations in single genes (“monogenetic diseases”) (WHO 2015; Kingsmore et al. 2011). Many of the genetic diseases known or suspected are rare or “ultra-rare” (by definition, rare diseases occur in fewer than 1 in 2,000 people, ultra-rare diseases in fewer than 1 in 2,000,000) (Hennekam 2011), but the total burden of such genetic diseases is significant, with researchers estimating that around 1% of the population, on average, has at least one condition associated with a single-gene disorder, and perhaps 4–10% of all pediatric hospital admissions are the result of single-gene disorders or chromosomal abnormalities (Dye et al. 2011; Kingsmore et al. 2011).

This description, however, hides the fact that a clear articulation of the “genetic disease” concept remains elusive. Part of the problem is that “disease” itself is a complex and contested concept (Murphy 2015); furthermore, the conceptual difficulties in untangling what it might mean to speak of any trait as “genetic” at the very least compounds the difficulties. Descriptions of genetic diseases usually rely on language to the effect that “abnormalities” or “defects” in the DNA (or in the chromosomes, etc.) lead to a disease state, but definitions relying on particular answers to what will count as “normal,” or what constitutes a “defect,” are also problematic and controversial (Amundson 2005).

It is worth distinguishing between diseases caused by so-called single-gene (monogenetic) diseases, those caused by chromosomal abnormalities, and complex diseases associated with variation in (many different) genes as well as variation in the environments encountered. In addition to single-gene disorders (and the smaller number of chromosomal abnormalities), many much more common medical conditions are said to “have a genetic component.” Some researchers estimate that 30% or more of pediatric hospital admissions are the result of diseases with a “strong” genetic component (McCandless et al. 2004; Dye et al. 2011). And many common diseases—e.g., heart disease, diabetes—are thought to be “partially” genetic; this is generally interpreted to mean that one’s overall genetic endowment is a risk factor for the disease, along with environmental factors (Craig 2008; McClellan and King 2010; Mitchell 2012).

This essay starts with a brief overview of some of the different ways that genes are referred to in the literature. Next, some of the important distinctions within genetic diseases will be outlined. Complications in the “genetic disease” concept will then be introduced, and
phenylketonuria (PKU, or “phenylalanine hydroxylase deficiency”) will be used as an example of a “classic” genetic disease and as an opportunity to reflect on the complexities of even relatively well-understood “simple” genetic diseases. Finally, the chapter ends with some further reflections on the genetic disease concept.

2. Genes in Contexts

It is traditional in genetics research to distinguish between an organism’s genotype and its phenotype. The genotype of an organism is the complete complement of genetic material—all of its DNA; note that for eukaryotes (organisms whose cells contain a membrane-bounded nucleus), this includes mitochondrial DNA as well. An organism’s phenotype, on the other hand, consists of all the measurable traits of the organism except its DNA sequence. So while, for example, the height of a plant is an aspect of its phenotype, so would be the concentration of a particular protein in a particular leaf of that plant. As with most distinctions in biology, there are fuzzy areas—for example, the way a particular chromosome is folded can influence which genes are expressed, what proteins get made, and so forth; is this folding pattern an aspect of the organism’s genotype or its phenotype? More generally, epigenetic traits (traits that modify gene expression at the molecular level) seem to rest right on the divide between genetic and phenotypic traits (Hanley et al. 2010).

DNA consists of a deoxyribose sugar and phosphate “backbone” linked to nitrogen-based “bases.” These bases, adenine (A), guanine (G), cytosine (C), and thymine (T), are the nucleotides, and each location on a DNA molecule where one of these bases can occur is a nucleotide site; the “genetic code” is a mapping of triplets of base-pairs (“codons”) to one of 20 amino acids, plus “stop” codons. When people speak of genes “coding” for proteins, they are referring to the process by which the amino acids that these triplets code for are assembled together to make particular proteins. Particular stretches of DNA are called nucleotide regions; these regions are simply a “mapping” convenience and can be entirely arbitrary. Famously, DNA forms a double helix; these helices themselves are wrapped tightly, and form chromosomes.

The idea of a “genetic disease,” and especially the idea of “single-gene disorders,” relies on there being a coherent “gene concept”—something that can be said to be “a gene.” But the “gene concept” turns out to be surprisingly contentious (see e.g., Moss 2004; Griffiths and Stotz 2006; Portin 2009). Genes are often thought to be functional nucleotide regions. The most obvious functional regions are those that code for proteins; codons that together specify the sequence of amino acids that get used in forming a protein (note in eukaryotes, most DNA is not involved directly in specifying sequences for protein synthesis). These proteins, consisting of many amino acids, are used in the cellular processes resulting in growth, reproduction, development, and the like. Other obvious functional regions include regions associated with gene regulation (these control how much of a particular protein gets produced); there are a number of different regulatory mechanisms (see e.g., Latchman 2011 for review).
Although these functional conceptions of genes are useful for understanding development generally, the most obviously relevant gene concept for thinking about genetic diseases may be the gene as a *difference maker* (see Waters 2007). Here, the main concern is not with the role played by the nucleotide sequence in development, but rather the locations on the genome where there is variation associated with phenotypic variation—that is, places where the presence of different *alleles* (different versions of a gene) are associated with different developmental outcomes. When people use the language of a “gene for” some trait (including diseases), this is the sense they are usually (if perhaps unwittingly) pointing towards—a place where some version of a gene is associated with some particular trait.

### 3. Genetic Diseases: A Brief Typology of Kinds

Before interrogating the “genetic disease” concept, it is useful to consider some of the different forms of genetic disease that are usually identified.

**Chromosomal abnormalities** identify the problematic feature at the level of the chromosome; these can include extra chromosomes (e.g., trisomy 21, which causes Down syndrome), fewer than the normal number of chromosomes (e.g., Turner syndrome, caused by the absence of one of the two sex chromosomes, leaving only a single X chromosome), deletions of part of a chromosome, duplications of part of a chromosome, rearrangements of various kinds (e.g., inversions of parts of a chromosome, or material on different chromosomes swapping places), or structural defects in the chromosome that make it susceptible to breaking (see NIH Fact Sheet: Chromosome Abnormalities).

**Complex diseases** (aka multifactorial disorders), in which both genetic variation at several different locations and particular environmental variations are thought to play a role in the development of the disease, include essentially all common chronic illnesses, along with most forms of mental illness (see e.g., Craig 2008; McClellan and King 2010; Mitchell 2012). Indeed, while it has proven more difficult to find particular gene variants associated with complex diseases than many researchers had hoped (see Manolio et al. 2009; McClellan and King 2010), it seems clear that genetic variation plays some role in the development and the particular clinical course of most diseases, including even classic infectious diseases (see Chapman and Hill 2012). For the reasons explored below, it is difficult to state precisely what makes something a “complex” disease with a genetic component, as opposed to a “genetic” disease that strongly interacts with particular environments. But in general, it seems that if particular alleles increase the disease risk significantly individually, the trend is to think of the disease in question as an ordinary genetic disease, whereas if no individual allele is responsible for any marked increase in the disease risk (but relative risk among genetically similar individuals still suggests an important overall genetic component of some sort), then the disease is usually classed as “complex.”

Single-gene diseases, as the name implies, are the result of some variation in a single gene—usually, in a nucleotide region that codes for a protein (or is part of a region that can code for several different proteins) or is part of a regulatory region. Diseases associated with single-gene variations are what are most commonly thought of as genetic diseases. As noted above, over 10,000 diseases in humans are associated with single-gene mutations or variants; most are quite rare. Single genes associated with diseases in humans can be classed according to the general pattern of inheritance that they show.

**Autosomal** genes are those that are on the *non-sex chromosomes* (i.e., on any chromosome *except* the X or Y). Diseases associated with *autosomal recessive* genes occur only when two copies of the mutant gene are inherited (one from each parent); *homozygotes* express the disease, but *heterozygotes* (who have only one copy) do not. Gene variants associated with autosomal
recessive disorders are fairly common—indeed, Gao et al. (2015) estimate that on average everyone carries one or two autosomal recessive mutations that, in homozygote form, would lead to complete sterility or death. Rare autosomal recessive genes associated with disease may persist in a population because selection against them is very weak—for an allele that is harmful only in the homozygotic form, it is unlikely that any two individuals will both have that rare allele, and so unlikely that the condition will be expressed (as the vast majority of children will inherit at most one copy of the allele).

More common autosomal recessive genes can be the result either of heterozygote advantage or the “founder effect” (drift). Taking the case of heterozygote advantage first, consider sickle-cell anemia. Sickle-cell anemia is the result of being homozygotic for the \textit{HbS} allele, a mutant form of the gene that makes hemoglobin (this is oversimplified: there are several different \textit{HbS} alleles with different consequences for hemoglobin production, and the clinical manifestation of the disease even in homozygotes is variable, etc. See Rees, Williams, and Gladwin 2010). Heterozygotes for the \textit{HbS} allele, however, are resistant to certain forms of malaria. In areas where malaria is common, heterozygotes have a strong fitness advantage. This results in an equilibrium; the frequency of the alleles in the population associated with sickle cell will depend on the strength of selection for heterozygotes (how much better heterozygotes do compared to homozygotes for the “normal” form of hemoglobin) and the strength of selection against homozygotes (so, for example, the frequency of “modifier” genes that protect homozygotes from the worst consequences of sickle-cell disease may also influence the allele frequencies in these cases; see Rees, Williams, and Gladwin 2010, 2023). The high frequency of cystic fibrosis in some populations has led researchers to suspect that the \textit{CFTR} allele (the mutation associated with cystic fibrosis) might be associated with heterozygote advantage; however, nailing down precisely what advantage heterozygotes might have that could explain the frequency and distribution has been difficult (currently, resistance to tuberculosis is the favored hypothesis; see Mowat and Werpachowska 2015).

The “founder effect” occurs when a population goes through a “bottleneck”—something that reduces effective population size to relatively few individuals. This can occur when, for example, migration leads a small number of people to a new region (or when small populations are cut off from continued migration in other ways), or when a disease or other natural disaster radically reduces effective population size in a particular region. Under these conditions, genetic variation in the population is reduced, and previously rare alleles may increase in frequency via genetic drift. Previously rare alleles associated with autosomal recessive disorders may, under those conditions, become relatively more common, thus increasing the frequency with which the disease occurs (see Chong et al. 2012 for review). The high frequency of the alleles associated with Tay-Sachs disease in the Ashkenazi Jewish population, for example, is generally believed to be due to genetic drift and not to any selective advantage of heterozygotes (Risch et al. 2003).

\textit{Autosomal dominant} alleles cause the disease in question in heterozygotes as well as homozygotes—only one copy of the allele associated with the gene is required for the disease state. \textit{Huntington’s disease} is a relatively common example of an autosomal dominant disease; despite its devastating consequences, the frequency of the allele associated with Huntington’s is relatively high, perhaps due in part to Huntington’s generally being a \textit{late-onset} disease that, historically, would have struck most people \textit{after} they had already reproduced (the mean age of the onset of symptoms is a bit over 40 years) (see Walker 2007).

\textit{Sex-linked genetic diseases} involve genes on one of the sex chromosomes (X or Y). X-linked recessive disorders are relatively common among men (chromosomal males), who only inherit one copy of the X chromosome (along with a Y chromosome), and much less common among women (chromosomal females), who inherit two copies (this is complicated somewhat by X
chromosome inactivation, the process by which one of the two X chromosomes is inactivated in females). Color blindness, for example, is the result of a mutation on the X chromosome that prevents the formation of certain photopigments; it is far more common in men than in women (color blindness in some form is present in perhaps 8–10% of men and only perhaps half of 1% of women) (see Neitz and Neitz 2000). X-linked dominant disorders are very rare; they are, however, more common among chromosomal females (who, inheriting two X chromosomes, are twice as likely to inherit one with any particular rare allele, though again, this is complicated by X-chromosome inactivation). Rett syndrome, for example, is usually thought of as an X-linked dominant trait. It is worth noting, however, that Rett syndrome occurs almost exclusively in females because it is almost invariably fatal in males—the differential activation of the two copies of the X chromosome in females provides some cells with the functioning MECP2 genes, whereas males have none (see “Rett Syndrome Fact Sheet”). Part of what the complexities of inheritance patterns in these cases highlight is the inadequacy of the terms “recessive” and “dominant” when dealing with sex-linked genes, as only women will have alternative alleles available at loci on the X chromosome. Y-linked diseases are rare, in part because the Y chromosome is relatively small and contains relatively few genes; most of these diseases involve infertility, and of course only affect chromosomal males (see e.g., Jobling and Tyler-Smith 2000).

Mitochondria are subcellular organelles that are (mostly) maternally inherited through the egg cell (though limited paternal inheritance, from the sperm cell, may be possible; see Duchen 2004). Mitochondrial diseases can be caused by mutations in the mitochondrial DNA (mtDNA); though the mitochondria genome is small, it seems to have a relatively high mutation rate (Duchen 2004; Taylor and Turnbull 2005). Because many physically distinct mitochondria are inherited, mitochondria within a cell can be genetically different from one another; because they replicate within, but in a way partially independent from, the cells that contain them, different cell lineages within an individual can inherit different mitochondrial populations (Collins et al. 2002; Duchen 2004). The inheritance pattern for mitochondrial diseases tends to be complex, in part because, as the above suggests, mitochondria in a cell behave as a “population” with respect to transmission (see Taylor and Turnbull 2005). “Classic” diseases associated with mitochondrial DNA include Kearns–Sayre syndrome—like many mitochondrial diseases, the typical clinical manifestation of this disease includes problems with muscle tissue, heart problems, and eye issues; it is caused by a “large-scale” deletion that knocks out several genes (Taylor and Turnbull 2005, see their Table 2 for a list of mitochondrial diseases). But mitochondria mutations are implicated in some cases of a large number of conditions, only some of which are specific to mitochondria (see Taylor and Turnbull 2005).

4. Genetic Diseases: Concepts and Complexities

As noted above, it is difficult to come up with a definition of “genetic disease” that adequately captures our ordinary understanding of the concept. Part of the problem is that every trait, including disease states, is the result of a complex developmental process that includes any number of different developmental resources. Part of what identifying something as a “genetic disease” does is to point towards a particular developmental resource (a “gene” or “genes”) in this process and to identify it as causally special, but explaining why we point towards genes in some cases but not others is tricky.

Consider a simple example: is lactose intolerance (lacking lactase persistence) a “genetic disease” (this example is based on Hesslow 1984; see also Smith 2007)? In the case of populations that have a tradition of raising dairy animals, almost everyone has alleles associated with lactase persistence (the ability to keep producing the enzymes necessary to digest the lactose
in milk after infancy), and consuming milk is a regular part of the culture (see, e.g., Ingram and Swallow 2007). Here, someone who lacks a functional version of the allele that, in that population, is associated with lactase persistence, will be lactose intolerant. And given that dairy consumption is a part of the culture’s usual diet, he/she will likely be identified as having a (medical) problem that can be tied to a particular variation in the genome—a genetic disease. But now consider a population without a tradition of raising dairy animals; in these populations, almost no one has alleles associated with lactase persistence, and dairy products are not normally consumed after infancy. In such a population, someone who, as an adult, nevertheless consumes a dairy product will get sick, but it would seem odd to blame his or her sickness on the lack of the lactase enzyme (since there was no reason to expect that he or she would have the enzyme after infancy). Rather, the (medical) problem the person has is more naturally thought to be that he or she ate something he or she ought not to have eaten, something that we would expect, in that population, to result in an illness. In the first case, a genetic difference from the relevant population seems explanatory; in the second case, an environmental difference from the relevant population seems to be doing the work. But in both cases, the illness results from both lacking the gene to make the relevant enzyme and consuming food with lactose.

In a somewhat similar vein, consider one of the class of inherited immunodeficiency diseases; these range from Severe Combined Immunodeficiency Syndrome (SCIDS—there are several different genetic disorders that result in this near-total failure to develop immune function; these are fatal in the absence of treatment) to conditions that result in an increased risk from only certain classes of infectious diseases (see e.g., Janeway et al. 2001, Chapter 11). These conditions are generally regarded as “genetic diseases.” But while AIDS is caused by the HIV virus, and so generally regarded as an infectious disease itself, people with the CCR5Δ32 allele are highly resistant to HIV infection; indeed, to date, the only person cured of HIV was treated for leukemia with a bone marrow transplant from a donor with the CCR5Δ32 allele (the patient, at last report, was still virus-free despite no longer taking antivirals) (see Hütter and Thiel 2011). It would seem at best very odd, however, to claim that HIV/AIDS was a genetic disease, caused by the lack of the CCR5Δ32 allele! However, the two cases are, on one description at least, very similar—an infectious agent is only problematic when combined with an immune system lacking certain elements, where those lacks are related to the absence of particular alleles. The difference between the two cases seems to be that most people have immune systems able to handle the infectious agents that people with SCIDS cannot, whereas the CCR5Δ32 allele is relatively rare, and so most people are susceptible to HIV.

More generally, as McClellan and King point out, genetic diseases are far more heterogeneous than usually thought, in a number of different ways, including at least:

- the same gene may harbor many (hundreds or even thousands) different rare severe mutations in unrelated affected individuals . . . the same mutation may lead to different clinical manifestations (phenotypes) in different individuals; and . . . mutations in different genes in the same or related pathways may lead to the same disorder.

(2010, 210)

McClellan and King are pointing out that the relationship between genes and diseases, even in cases of genetic diseases normally identified as straightforward single-gene disorders, is “many-many” rather than “one-to-one.” Different mutations in the same region (the same gene) can lead to the same disease (the same phenotype), as can mutations in different regions (in different genes); the same illness can be associated with many different genes. Indeed, in some cases
a disease with the same clinical features may be associated with either a particular gene or a particular environment. Further, the same mutation—the same change in a particular gene—can lead to different phenotypes, from severe forms of a particular disease to apparently normal phenotypes (no clinical manifestations of the disease); the same gene can be associated with many different forms of an illness (or with no illness at all).

PKU (phenylketonuria or “phenylalanine hydroxylase deficiency”) provides a good entry into these issues, in part because it has been intensely studied and is relatively well-understood (see, e.g., Williams, Mamotte, and Burnett 2008 and cites therein). PKU is (usually thought of as) a genetic disease caused by having two copies of a mutated human phenylalanine hydroxylase gene (the PAH gene), where both copies fail to produce a (sufficient quantity of) properly functional phenylalanine hydroxylase enzyme (the PAH enzyme). People with PKU therefore lack the ability to properly metabolize the amino acid phenylalanine (Phe); untreated, this can lead to the “accumulation of toxic by-products of Phe metabolism,” along with shortages of some key metabolites usually produced (primarily Tyrosine, Tyr) (see Williams, Mamotte, and Burnett 2008). Untreated PKU is associated with a range of problematic phenotypic outcomes, including severe deficits in cognitive development and other cognitive problems, and a range of skin and bone problems. Treatment consists mainly of a special diet, very low in phenylalanine, with supplemental tyrosine, although drugs to help metabolize phenylalanine are increasingly part of standard clinical practice (see Vockley et al. 2014). Because treatment is more effective the earlier it is started, most countries test all newborns soon after birth for PKU (along with a number of other disorders). Indeed, PKU screening is generally regarded as the first universal newborn genetic screening program; newborn screening for PKU was first deployed in the 1960s, and by the 1970s newborn screening for PKU (along with some other disorders) had become standard practice in most developed countries (see Brosco and Paul 2013).

The above provides the “sketch” for the “standard” story about PKU. Although there is nothing actually wrong with this story, it is oversimplified in important ways, and perhaps gives a misleading impression of the relationship between both the relevant genetic mutations and the ability (or lack thereof) to metabolize phenylalanine, and the inability to metabolize phenylalanine and phenotypic effects of that inability. Indeed, the relationships here are complex in just the ways that McClellan and King (2010) suggested: many different mutations can give rise to “the same” disease state, the same mutations are associated with different metabolic activity levels, and the same metabolic activity levels are associated with different phenotypic outcomes.

The PAH gene codes for the PAH enzyme, a protein made up of 452 amino acids; as might be expected, there are many ways for things to go wrong and many different mutations in the PAH gene that are associated with PKU (more than 500 have been identified to date; see Williams, Mamotte, and Burnett 2008, 33). The majority of mutations in PKU individuals seem to be missense mutations—places where the “wrong” amino acid was inserted into the protein (see Williams, Mamotte, and Burnett 2008, 33); as suggested above, different missense mutations are associated with different proteins, with different levels of enzymatic activity; many of these missense mutations seem to be problematic largely because they cause the proteins to misfold and (perhaps) to be more rapidly degraded (see Scriver and Waters 1999). Other mutations—nonsense mutations (where a mutation results in a “stop” code and prevents the formation of the full protein), frameshift mutations (where a deletion or insertion of a nucleotide results in a change to all downstream nucleotide triplets, and hence many changes in the amino acids produced), etc.—result in something more like a total lack of enzymatic activity, as even if a protein is produced, it is too dissimilar to the PAH enzyme to do any of the same work (see Williams, Mamotte, and Burnett 2008, 33).
As Scriver and Waters (1999) note, “there are many instances of discordance between the mutant PAH genotype, its predicted effect on enzyme function, and the associated metabolic phenotype” (268). As noted above, different mutations in the PAH gene are statistically associated with different levels of enzymatic function, some of which can be predicted from the protein formed, but this association shows significant variation. The mechanisms by which “missense” mutations result in the loss of enzymatic function in the case of PAH enzyme are complex, and differences in the “chaperone” systems (chemical systems that help the protein fold into the correct final form) between individuals may be responsible for the same PAH mutations being associated with different levels of enzymatic function (see Scriver and Waters 1999, 268–270). Furthermore, the same level of enzymatic function can be associated with different metabolic outcomes—while two people might share PAH enzymes that are equally unable to metabolize phenylalanine, one might for example be better able to eliminate excess phenylalanine via other metabolic pathways (Scriver and Waters 1999, 269). And even if two individuals have equal metabolic responses to phenylalanine, the effect of that metabolic response can be different; differences in the particulars of the blood-brain barrier, for example, can mediate the influence of excess phenylalanine on cognitive development (Scriver and Waters 1999, 268, 270). The result of this is that “patients, even sibs, sharing identical mutant PAH genotypes could have greatly different cognitive and metabolic phenotypes” (Scriver and Waters 1999, 268).

Along with the large number of possible errors in the PAH gene, in thinking about the many-many relationship between genes and disease states, it is interesting to reflect on tetrahydrobiopterin (BH₄) deficiency, a much rarer genetic disease (PKU is present in perhaps 1:10,000 live births; tetrahydrobiopterin deficiency is present in perhaps 3:1,000,000 or so, though the frequency varies significantly by region; see Blau, Bonafé, and Blaskovics 2005). BH₄ is necessary for the proper metabolism of phenylalanine, and deficiency can result in hyperphenylalaninaemia, the same excess of phenylalanine that characterizes PKU; mutations in one of a number of genes can result in this BH₄ deficiency, and, like mutations in the PAH genes, the impacts of these mutations on phenylalanine metabolism can range from mild to severe (see Blau, Bonafé, and Blaskovics 2005). Untreated, the phenotypic impacts of tetrahydrobiopterin deficiency are broadly similar to PKU; indeed, in the 1970s, it was common to refer to tetrahydrobiopterin deficiency as a kind of atypical PKU (see, e.g., Kaufman et al. 1975; Curtius et al. 1979; see Ponzone et al. 2004 for discussion). In recent years, however, it has become standard practice to distinguish PKU (caused by mutations in the PAH gene) from tetrahydrobiopterin deficiency, both because they have a different cause and because different treatments are recommended (BH₄ replacement therapy is standard for tetrahydrobiopterin deficiency, sometimes with and sometimes without dietary phenylalanine restriction; see Ponzone et al. 2004; Blau, Bonafé, and Blaskovics 2005; Blau, van Spronsen, and Levy 2010). However, the fact that some forms of “traditional” PKU also respond well to BH₄ therapy (for some patients, increasing BH₄ levels improves PAH enzyme function impaired by errors in the PAH gene; see Blau and Erlandsen 2004; Blau, van Spronsen, and Levy 2010) makes this distinction a little less clear-cut than it is sometimes made out to be.

Are PKU and tetrahydrobiopterin deficiency best thought of as two variants of the same disease (“hyperphenylalaninaemia”), or are they best viewed as two different diseases that share some biological pathways and have some broadly similar phenotypic (clinical) outcomes? Is a case of PKU caused by the complete absence of a functional PAH enzyme (say, from a “non-sense” mutation that stops transcription too early), a severe form of the same disease as a case of PKU associated with reduced (but still functional) PAH enzyme activity, or are these different diseases? In individuating “genetic diseases” should we be focused on the gene whose function is being disrupted (all and only disruptions of the PAH gene are the same disease, PKU), on
the particular form of the disruption (all and only similar failures of PAH enzyme are the same form of PKU), or on the downstream metabolic and phenotypic consequences (all and only conditions that result in the buildup of excess phenylalanine are PKU)? Answering these questions would seem to demand making decisions about the proper use of language, rather than discovering straightforward facts about the world; depending on our particular interests and research agendas, either answer seems defensible. Although one might avoid the conclusion that the same disease can be caused by different mutations in the same gene, or by mutations in different genes, by declaring, as a matter of fiat, that genetic diseases are to be individuated on the basis of the specific mutation associated with them, doing so would merely elide the force of the “many-many” problem.

5. Conclusion: Reflections on the Genetic Disease Concept

Of something purported to be a genetic disease, we can ask at least two questions: How likely is someone to have the disease in question if they have the genetic mutation in question? and How likely is someone to have the disease in question if that person lacks the genetic mutation in question? “Ideal” genetic diseases are those in which a particular mutation makes the presence of the disease very likely (nearly certain), and in which the clinical manifestation of that disease is very rare (all but absent) in the absence of the genetic mutation in question. Smith suggests an “epidemiological” account of “genetic disease,” where, “intuitively,” (1) “If a disease is genetic, this must mean that those with the gene are more likely than not to develop the disease,” and (2) “If a disease is genetic, this must mean that cases of disease more likely than not causally involve the gene in a significant way” (2007, 97). Smith goes on to unpack the work being done by notions of causation in the intuitive account, in order to produce a more precise “minimally epidemiological” account of genetic disease, where (1) gets interpreted in terms of a “Population Etiologic Fraction (PEF)”—the fraction of individuals with the disease “whose disease causally involved the gene” and (2) gets cashed out as an “Attributable Risk (AR)”—the fraction of people with the gene “whose disease causally involved the gene” (Smith 2007, 100–101; see also Smith 2001). Smith suggests that if both numbers are greater than 50%, the minimal epidemiological account of something’s being a genetic disease has been met (Smith 2007, 102).

As Smith notes, the trouble with these accounts is that, in many cases, we simply don’t know either the “attributable risk” or the “population etiologic fraction” (2001, 2007, 104). For many “classic” genetic diseases, the belief that everyone, or almost everyone, with the relevant genes would reveal the standard clinical manifestations of the disease was only challenged with the rise of genetic testing; for example, when testing for the most common mutations associated with cystic fibrosis was established, some individuals were discovered with mutations usually associated with the classic forms of the disease, but who were asymptomatic or only mildly symptomatic (see Zielenski 2000; Doull 2001). More generally, as Smith points out, for cystic fibrosis every possible combination of clinical symptoms, sweat chloride level, and genotype has been identified (Smith 2001, 21).

The “population etiologic fraction” is even more likely to be controversial, because, as noted above, for many conditions researchers identify the disease with the cause; when a different causal pathway is uncovered, it is regarded as generating a different disease, even if the clinical manifestations are broadly similar. If we simply declare that nothing is PKU unless it is associated with a mutation in the PAH gene that results in functional changes to the PAH enzyme, then of course the “population etiologic fraction” will be very high indeed (100%, by fiat). If we individuate diseases in terms of their most common clinical manifestations, then more diseases will be caused by a number of different factors, where some are genetic and others
environmental. But again, which of these approaches is to be preferred would seem to depend on our particular projects (so, for example, the different projects of developing diagnostic tools, developing treatments, and developing classificatory schemes might suggest different ways of individuating diseases). Note well that which projects seem most plausible and worth pursuing will be sensitive to any number of factors—cultural, political, economic, and so forth.

The difficulty in specifying what, precisely, makes something a genetic disease emerges in part from the complexity of the biological world. It is difficult to specify what makes something a disease and what constitutes health. The role played by nucleotide sequences in development are varied and complex, and it is difficult to say what makes some nucleotide sequence a “gene.” The genetic disease concept would seem to rely on a distinction between “normal” and “abnormal” genetic sequences that is hard to make precise (and perhaps hard to defend). Arguments about whether to count diseases with partial genetic etiologies as genetic diseases—whether “complex” diseases are a kind of genetic disease, or something else entirely—seem to depend more on the researchers’ outlooks than anything else.

For all that, while making the distinction precise may prove difficult, the genetic disease concept is firmly entrenched in biomedicine. Although even some of the most “classic” genetic diseases have proven to be far more complicated than anyone would have predicted, those diseases are still regarded as genetic diseases. If we need to adopt a method for distinguishing genetic diseases from other kinds of diseases, Smith’s approach (2001, 2007) seems the most adequate attempt so far. It is not perfect, but it does seem to capture at least some of the key intuitions behind the distinction.

References


Further Reading

The National Center for Biotechnology Information, part of the National Library of Medicine, maintains an excellent collection of materials related to particular genetic diseases (“Genes and Diseases”) at http://www.ncbi.nlm.nih.gov/books/NBK22183/.
