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50 whys to look for genes: Pros and complications

Peter J. Taylor
peter.taylor@umb.edu

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Pros and complications

PETER J. TAYLOR

GRADUATE PROGRAM IN CRITICAL AND CREATIVE THINKING
University of Massachusetts, Boston, MA 02125, USA
http://scholarworks.umb.edu/cct_sicw/12

50 whys to look for genes: Pros and complications

Peter J. Taylor
Science in a Changing World graduate track,
http://www.stv.umb.edu/
University of Massachusetts, Boston
peter.taylor@umb.edu

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Abstract

“Treating the audience as capable of thinking about the complexities that surround the application of genetic knowledge” was the tagline of a series of daily blog posts made over seven weeks in the fall of 2014, posts that included extended quotes from the recently published *Nature-Nurture? No* (Taylor 2014). This working paper is a compilation of those posts.

Prologue

Waiting at the checkout yesterday, I noticed a special issue of Time: “How DNA shapes your life (Figure 0.1). “Having tried to harness the power of DNA for decades,” the introduction begins, “we’re finally getting somewhere” (Park 2014, N.p.). The special issue and its articles are clearly optimistic, even boosterish, without much nuance, at least in their titles for I have yet to read and digest the substance and style of the articles. I did, however, start to mull over what it would take to make a special issue that delved into the range of meanings of genes and genetic, that treated the audience as capable of thinking about the complexities that surround the application of genetic knowledge. (Analogous to my thinking many years ago after reading Sally Ride’s book for children about the space shuttle about how to explain why astronauts begin to feel weight as they return from orbit. Ride said it is because of gravity and getting close to the earth, which is not the reason—see the first part of Taylor 2002.) This led me to start listing the variety of reasons one might look for the genetic basis of something and, for each, think about issues that confound or complicate the situation or claims being made. (My previous list of different meanings of genetic helped; Taylor 2013a). As the list got longer (it is up to 40 already), I thought of the title and decided to begin a series of posts.

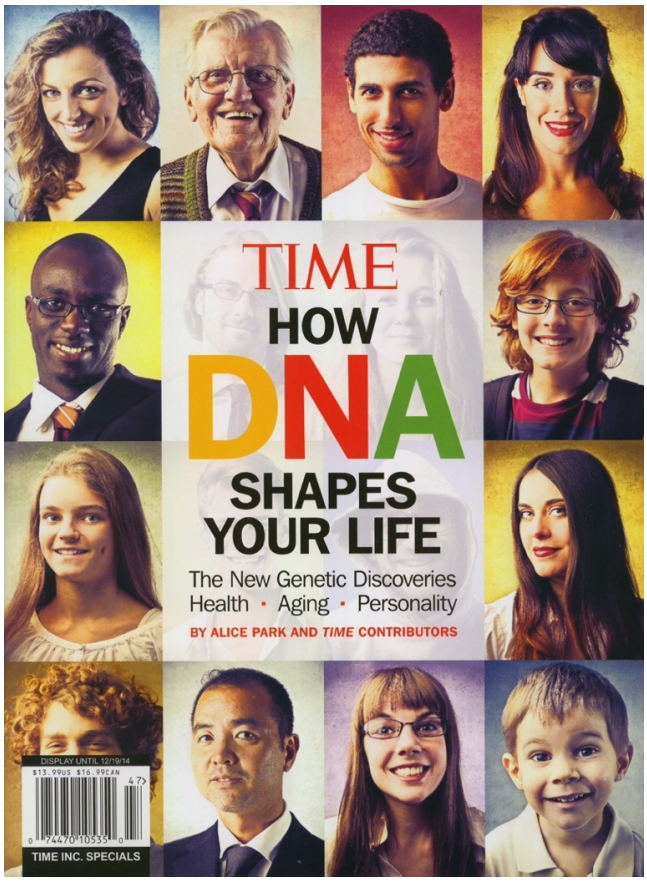


Figure 0.1: Cover Image. “How DNA shapes your life.” 2014 Special Issue of *Time Magazine*.

Just how these will be organized is not yet clear[1], but one important distinction will be between "two aspects of heredity—the transmission of traits to offspring—…how does an offspring *develop* to have the trait in question at all, e.g., its eye color, and how does the outcome of the development at some point in the lifespan *differ* from that person to the rest of the family or population" (Taylor 2014, p. 2).

At the same time, the length of the list got me thinking about Atsushi Akera's picture of the history of research (in his case, around computers) where "[t]ensions and differences often produced redundant, over-ambitious, and incoherent research programs" (2006, p. 10). History of technology, he contends, needs to value the study of failure and to "make the notion of failure relative if one's goal is to document the less linear paths of innovation" (p. 338). If that image fits genetic research, we might puzzle over why the public image of genetics is of a "relatively smooth process."

Anyway, stay tuned for the whys, the pros, the complications, and exploration to organize the list and conceptualize its length.

[1] Subjects in brackets at the end of each post were defined after all the posts were finished. The map at the end of the paper shows the distribution and overlap of these subjects.

1. Understand how the living world operates (at molecular level)

One reason to look for the genetic basis for an observed trait is to understand how the living world operates at molecular level.

Complication

A complication is evident in the case of phenylketonuria (PKU) in humans. PKU has been shown to be associated with having two copies of a malfunctioning gene for the enzyme phenylalanine hydroxylase (PAH). The cognitive development of such individuals is extremely impaired by the level of phenylalanine present in normal diets. However, the detection of PKU in newborns is possible on the basis of a biochemical test, which was widely applied before the genetic basis was known. Biochemical screening, not genetic, continues to be the basis for initiating the diet needed to prevent the cognitive impairment that had been associated with PKU. The more general issue is, if we want to understand how the living world operates at molecular level, when do we need to go beyond the biochemistry to look for the genes?

[Therapeutics & other interventions]

2. Identify presence of risk factors

If presence of a section of DNA—a single-nucleotide polymorphism (SNP) (Wikipedia N.d.*g*)—increases the odds of a disease, then look for that section in people and provide them that information.

Complication

As described in an article in *The New York Times* (Grady and Pollack 2014), the information might not translate into remedial action or not into action that is within the resources of the person and their community of care and support. Withholding such information once it is available is seen by some as paternalistic (see controversy over study of Huntington's Disease in a Venezuelan community (The Understanding Evolution Team N.d.)). At the same time, it could also be seen as paternalistic to develop the means to provide the information without developing the capacity to provide the care and support and without involving in decision-making about research those who will be affected by the results.

[Diagnosis by genetic type/sequence]

3. High heritability => genetic influences > environmental

If heritability is high for a given trait, it might seem that genetic influences outweigh environmental and resources for research to understand the trait are better devoted to looking for the genes rather than the environmental influences.

Complications

There are many complications to this line of thinking, including the "it might seem" reasoning and the rise of a new concept of heritability that shares the same name as heritability in the classical sense (as collated in the SNPedia (N.d.) heritability table of estimates). These issues are discussed in Taylor (2014, pp. 31-32 and pp. 124-5 respectively), but the complication to be discussed here concerns *underlying heterogeneity*. From Taylor (2014, pp. 19-20):

> Claims that some human trait, say, IQ test score at age 18, shows high heritability derive from an analysis of data from relatives. For example, the similarity of pairs of monozygotic twins (who share all their genes) can be compared with the similarity of pairs of dizygotic twins (who do not share all their genes). The more that the former similarity exceeds the latter, the higher the trait's *heritability*. Researchers and commentators often describe such calculations as showing how much a trait is *heritable* or *genetic*. However, no genes or measurable genetic factors (such as alleles, tandem repeats, or chromosomal inversions) are examined in deriving heritability estimates, nor does the method of analysis suggest where to look for them.
>
> Moreover, even if the similarity between twins or a set of close relatives is associated with the similarity of yet-to-be-identified genetic factors, *the factors may not be the same from one set of relatives to the next, or from one environment to the next*. In other words, the underlying factors may be *heterogeneous*. It could be that pairs of alleles, say, AAbbcbDDee, subject to a sequence of environmental factors, say, FghiJ, are associated, all other things being equal, with the same outcomes as alleles aabbCCDDEE subject to a sequence of environmental factors FgHiJ (see [Figure 3.1] for the case of human twins where both members of each pair are raised in the same household). If the genetic and environmental factors underlying the observed trait are heterogeneous, what can researchers do on the basis of a heritability estimate?

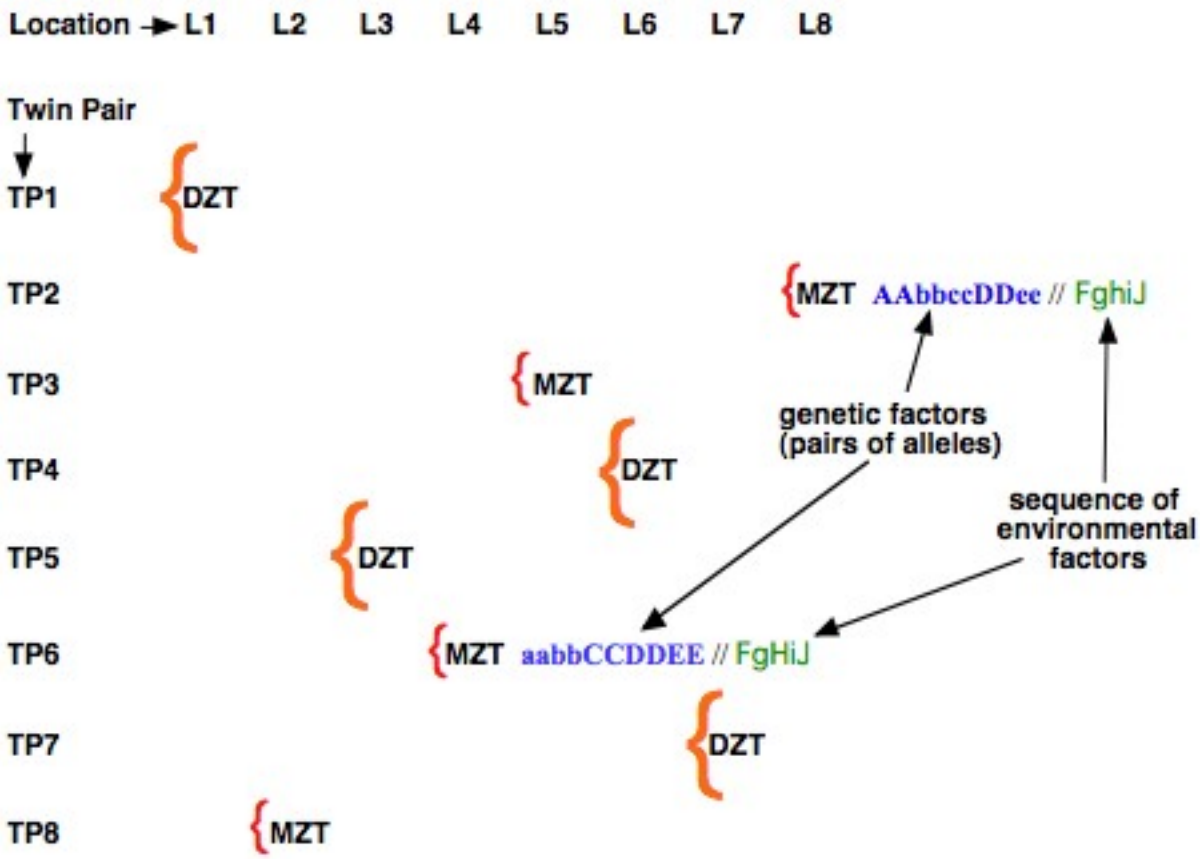


Figure 3.1 Factors underlying a trait may be heterogeneous even when identical (monozygotic) twins raised together (MZT) are more similar than fraternal (dizygotic) twins raised together (DZT). The greater similarity is indicated here by smaller size of the curly brackets. The underlying factors for two MZT pairs are indicated by upper- and lowercase letters for pairs of alleles (A-E) and the environmental factors to which they are subject (F-J).

[Variation within & between groups]

4. Understand the basis of traits

Since the rediscovery of Mendel's laws, it has been common to talk about genes for xx, where xx could be feeblemindedness, IQ, sports ability, procrastination, homosexuality, divorce, crime, fidelity, conservatism, liberalism, schizophrenia,... (You choose xx; see what you get when you Google "Is there a gene for xx.")

Complications

1. Is the trait a well-defined quality or condition? (see e.g., Poland 2004 on 'schizophrenia");

2. What is the evidence that the trait is determined by genes (e.g., if based on pedigrees, have they taken social/environmental conditions into account when these run in families too) and how general are these genes (e.g., extending Brunner syndrome beyond the Dutch family in which it was identified (Wikipedia N.d.*c*);

3. If a mutant gene is identified associated with an abnormal trait (e.g., for extra digits), it does not then follow that the absence of the mutant explains the normal trait (i.e., 5 digits); and

4. Using research that exposes mutant genes associated with abnormal traits leads one to think about complex characteristics developed through a lifetime of social interaction in binary terms, moreover, with one side of the binary being abnormal (e.g., think about genes for homosexuality, but not genes for heterosexuality, and think about sexuality as a binary not a diversity).

[Development & functioning of organism]

5. Entry points into study of development

Since the late 1800s—well before advances in genetics and molecular biology—developmental biologists have been studying the mechanisms through which a single cell divides into multiple cell types and gets arranged into tissues, organs, and the organism's overall form (Gilbert 2013). Genetic knowledge and technologies [provide] a productive strategy to work towards teasing open the complexities of development (Taylor 2014, 1-3).

Complications

The first is really a clarification. The term "entry-point" is used to distinguish from ideas that one could start from genes as the "blueprint" or "information" from which all else in the development of the organism follows. To appreciate this consider the following (Taylor 2014, p. 2):

> When it is said that a person resembles their parent, two aspects of heredity—the transmission of traits to offspring—are being raised: how does an offspring *develop* to have the trait in question at all, e.g., its eye color, and how does the outcome of the development at some point in the lifespan *differ* from that person to the rest of the family or population. Difference can. be studied without providing much insight about development. For example, the eyes of fruit flies, normally red, are sometimes white. Biologists identified the location on the chromosomes that corresponds to the white-eye mutation early in the 1900s and later investigated the pigment-formation metabolic pathway and the enzymes involved as fruit fly eyes develop the normal or mutant color. Such knowledge says little about how eyes develop. Even on the narrower question of how eyes get to have color, a lot has to be known already about the development of the eye as a whole to make sense of how and when during the fly's development the enzyme produces color in the eye.

Nevertheless, "[b]iologists often study abnormalities in order to gain insight about typical processes of development" (p. 2), and this is where looking for mutant genes that alter development can be helpful. The second complication then is that abnormalities not tied directly to genes can be studied "in order to gain insight about typical processes of development" (p. 2). Continuing from Taylor (2014, p. 2):

> In Swyer syndrome, for example, a child with XY chromosomes has female, not male, external genitalia. The influence of estrogen and progesterone on development is illuminated by the finding that, if these hormones are administered at puberty, breasts can develop and regular menstruation can occur (Michala et al. 2008).
>
> Variation under a more or less normal range of conditions can also help biologists understand typical development. The age at which a baby comes to walk, for example, varies according to whether it sleeps on its back or stomach, has been swaddled or carried around in a sling, and so on, and this variation has been related to the timing and degree to which the baby uses its upper body muscles (Fausto-Sterling 2014).

[Development & functioning of organism]

6. Genetic = hard to change

A gene passed to you from a parent is in every cell of the body that develops. If it has an effect on your traits, there is no way to expunge it from every cell in order to eliminate that effect.

Complication

The immutable gene, even when that gene has severe implications for the body, is insufficient to dictate the social implications for the person. Someone I came to know with muscular dystrophy was, in the 1960s, what we now call mainstreamed at school at his mother's insistence. High school friends who went on to university with him initiated a pattern of what we now call independent living that continued as his physical condition required sleeping in an iron lung. Meanwhile, he worked as a counsellor first for students then at centers for the disabled and became a parent, living decades beyond the expected 20 or so years for a male at that time with muscular dystrophy, particularly Duchenne muscular dystrophy (Wikipedia N.d.*e*). The gene mutation on his X chromosome never stopped having its effect and the social support he required was not simple, but a fulfilling life was possible.

[Development & functioning of organism]

7. To explain innate behaviors

A behavior that is innate occurs without being learned. As long as we can assume that the environment is sufficient for the organism to survive, this independence from learning might lead us to look for the genes that determine the trait.

Complications

Behaviors still have to be developed—they are not evident in the fertilized egg! Investigations of development show that behaviors that are fixed in normal circumstances can still be changed. For example, as Anne Fausto-Sterling describes, an innate behavior of rat pups is to crawl to their mother's teats after birth. Experimental studies have shown, however, that if the mothers are fed peppermint while pregnant, the newborn rat pups crawl towards the peppermint taste even if that takes them away from their mothers. We still have to explain the development of the innate behavior of pups crawling towards a taste that is familiar, but the experiment shows us the value of not simply looking at genes when elucidating development of innate behaviors. (It also invites us to imagine changes in the environment that render changeable behaviors that we had thought were universal to the species.)

[Development & functioning of organism]

8. Differences between groups not well explained by environmental factors

(The quotes to follow are from Taylor 2014, 18-19.)

> [A]ccording to the current consensus, heritability of IQ test scores is high (Neisser et al. 1996, but see Turkheimer et al. 2003, Nisbett et al. 2012). Persistent large differences in average IQ test score. exist between racial groups (but with recent decreases, Nisbett et al. 2012). Many human behavioral geneticists and psychometricians (analysts of data from personality and educational tests) are prepared to entertain a two-part argument: the high heritability of IQ test scores within racial groups *coupled with* a failure of environmental hypotheses to account for the group differences supports explanations of mean differences in terms of genetic factors (e.g., Jensen in Miele 2002, 111ff).

Complications

> The specific factors still have to be elucidated, so "support" may be read as "lends plausibility to the belief that they exist."
>
> There has been some success using regression analysis to identify associations between environmental factors and differences between the mean test scores for racial groups (Fryer and Levitt 2004).
>
> Flynn (1994) has pointed to large gains in average IQ test score between generations (now called the "Flynn effect"). No environmental factor, or composite of factors, such as diet or education level, has been shown to be strongly associated with these generational differences [but see above]. By [the logic of the two-part argument] we would have to entertain explanations of *generational* differences in terms of genetic factors, but we know that the changes in gene frequencies in a human population over one generation are negligible. There must be a hole in the logic of the two-part argument, but where is it? If we were to find the hole, would that help us explain large differences between generations in a high heritability trait such as IQ test score? These questions constitute the *IQ paradox* of Dickens and Flynn (2001).

[Variation within & between groups]

9. To distinguish among multiple environmental factors

In situations where multiple environmental factors seem to influence a human trait but a genetic variant exists, which may be quite rare in the population, that is associated with one of the environmental factors, then "Mendelian randomization" gives us as close to a controlled experiment as is possible. (The quotes to follow are from Taylor 2014, 144ff.)

> Mendelian here refers to the existence of variants at some locus on the gene that are associated with increased levels of the risk factor [and r]andomization refers to other risk factors having no association with the presence or absence of that variant (Davey Smith and Ebrahim 2007). It turns out that for four CRP variants, each associated with up to 30% higher CRP levels, no association with coronary heart disease has been found (C Reactive Protein Coronary Heart Disease Genetics Collaboration 2011).
>
> CRP may be thought of as an environmental factor possibly associated with the medical trait in the sense that CRP levels can be altered by medication. Mendelian randomization can also be used to investigate hypotheses about environmental factors in a more conventional sense. Consider the apparent association of moderate alcohol consumption with reduced incidence of coronary heart disease (Davey Smith and Ebrahim 2007, 344ff). Alcohol consumption is also associated with other factors associated with coronary heart disease, such as age, smoking, and an increased level of protective high-density lipoprotein. Moreover, nondrinkers may include people who have stopped drinking because of deterioration in their health. To disentangle these factors, we can look at Japanese populations that have a high frequency of a variant of an enzyme aldehyde dehydrogenase (ALDH2). This variant makes the after-effects of drinking very unpleasant. The average alcohol consumption of these people is low for people who are homozygous for the variant and intermediate for those who are heterozygous. The variant is not associated with—is randomized with respect to—age and smoking, so these factors are not involved in any association that remains between coronary heart disease and the ALDH2 variant—as a proxy for alcohol consumption. It turns out that there is an association between the variant and lower levels of high-density lipoprotein, which supports the causal status of moderate alcohol consumption as a protective factor for coronary heart disease (i.e., associated with a reduced incidence) through the effect of alcohol consumption on levels of high-density lipoprotein.

Complications

> Davey Smith and Ebrahim (2007) provide a review of other examples and address potential limitations of Mendelian randomization.
>
> [In order for] application of the results—assuming the results show that the modifiable factor is causally associated with the trait—the factor must be reduced in the population by means that do not exacerbate the other factors associated with the trait. The means of securing that reduction may involve a clinical focus on treating the subset of individuals who have high levels of the factor in question or a public health focus on reducing the average levels of the factor in the population. (The tension between a clinical and public health focus is longstanding in epidemiology and applies not only to the results of Mendelian randomization; Rose 2008 [1992]).

[Variation within & between groups]

10. Identify risk factors (using GWA studies)

If presence of a section of DNA—a single-nucleotide polymorphism (SNP) (Wikipedia N.d.*g*)—increases the odds of a disease, then look for genes close to the SNP, investigate the enzymes associated with the gene and use that as an entry point to investigation of the etiology of the disease, then try to design drug therapies to counteract any undesired function of those enzymes or their subsequent effects. (The quotes to follow are from Taylor 2014, 141-2.)

The search for SNPs associated with disease can be done by Genome-Wide Association (GWA) studies, which

> have two parts: a) compare a group of individuals—the *case*—who have a disease or other trait with a group of individuals—the *control*—who do not have the trait but match the case in their distribution of other traits; and b) identify places (loci) on the genome that are significantly more frequent in the case compared with the control. The loci in GWA studies are SNPs (single-nucleotide polymorphisms), which are not the causal genetic factors for the trait, but are simply somewhere close to those factors on the genome. The case and control groups are large (up to around 200,000) and a huge number of SNPs (up to around 1 million) are assayed.
>
> The first successful GWA study was published in 2005. Soon variants were identified that were associated, at least in the defined populations from which the case and control groups were drawn, with increased incidence in diseases such as diabetes, heart disease, and cancers (Khoury et al. 2007).

Complications

> As it has turned out, however, for loci where variants have a statistically significant association with some medically significant trait, that association corresponds to a small increase in incidence of the trait (McCarthy et al. 2008). Expressed in terms of odds, the odds of an individual with the variant having the trait is generally no more than 1.5 times the odds of having it when the variant is not present. Moreover, even when many such associations are considered jointly, most of the variation in the trait remains unaccounted for (Ku et al. 2010...).
>
> The hope had been to expose variants corresponding to a major increase in incidence of the trait, and from that to gain insight into the mechanisms of the disease. Some researchers claim new biomedical insights based on variants corresponding to a small increase (Wheeler and Barroso 2012) or expect the yield from GWA studies to improve once the causally relevant stretches of DNA near the SNPs are identified.
>
> Notwithstanding these claims or hopes of new insights, there is active debate on the implications of the difficulty in identifying causally relevant genetic variants through GWA studies (Couzin-Frankel 2010). Some researchers go from the observation that many variants have a small effect (that is, an association with a small increase in incidence of the trait) to a conjecture that future advances in the understanding of a disease will come from finding rare variants (alleles) that have a strong effect (McClellan and King 2010).
>
> Genetic heterogeneity is built into this conjecture in the sense that, even if insight about mechanisms emerged from an examination of the strong effect of the rare variant, most of the cases would not be associated with the rare variant. Moreover, the detection and identification of variants is obviously complicated by genetic heterogeneity in its various

forms (e.g., mutations in a gene can occur at a variety of points in the gene, the clinical expression of such mutations can vary significantly, and different genetic variants may be expressed as the same clinical entity...).

[Diagnosis by genetic type/sequence]

11. Eliminate the distinction between familial and hereditary cancers

Medical oncologists describe a cancer or likelihood of cancer as *familial* if a family genealogy shows, say, breast or ovarian cancer in female relatives. They would suspect a gene passed down but not know its identity. A *hereditary* cancer or likelihood of cancer is when a person is shown, by genetic testing, to carry a specific gene, such as BRCA1 or BRCA2, that has been linked to a much higher frequency of incidence of the cancer. Medical oncologists suggest that the distinction between familial and hereditary cancers will eventually be eliminated as the genes for the familial cancers are identified.

Complications

a) the association with the identified gene ”correspond[ing only] to a small increase in incidence of the trait” (see Chapter 10), perhaps because

b) the factors underlying the cancer may not be the same from one set of relatives to the next (see Chapter 3), and/or

c) “the information [about carrying a gene] might not translate into remedial action or not into action that is within the resources of the person and their community of care and support” (see Chapter 2).

[Diagnosis by genetic type/sequence]

12. Similar varieties respond similarly in similar locations

(The quotes to follow are from Taylor 2014, 95ff.)

> In agricultural trials, where a number of varieties or animals or plants can be raised or grown in multiple replicates in many locations, varieties can be grouped by similarity in responses across all locations using techniques of cluster analysis (Byth et al. 1976). Varieties in any resulting group tend to be above average for a location in the same locations and below average in the same location. The wider the range of locations in the measurements on which the grouping is based, the more likely it is that the ups and downs shared by varieties in a group are produced by the same conjunctions of measurable factors [genes and environmental factors].

> For example, imagine a group of plant varieties that originated from particular parental or ancestral stock that is more susceptible to plant rusts (a form of parasitic fungi), and that these varieties had a poor yield in locations where rainfall occurred in concentrated periods on poorly drained soils. The obvious hypothesis about genetic factors modulated by environmental factors is that these varieties share genes from the parental stock that are related to rust susceptibility and this susceptibility is evident in the measurements of yield in locations where the rainfall pattern enhances rusts. Through additional research to compare the variety and ancestral genomes, it may be possible to identify specific sets of genes that are shared, to investigate whether and how each one contributes to rust susceptibility, and to use that knowledge in planting recommendations for locations like those observed in the trial and for subsequent research that might extend beyond the observed varieties and locations.

Complications

> It becomes more difficult to distinguish groups of varieties by similarity of responses across locations when varieties are observed in only a few locations or when the locations are not the same from one variety to the next. [This approach] becomes infeasible when analyzing measurements from studies of human twins because such studies have only two replicates (twins) in one or at most two locations (families).

[Selection—artificial & natural, Variation between & within groups]

13. Genetics is “the future of medicine”

> [A] deeper understanding of the fundamental mechanisms of life *promises* to lead to an era of molecular medicine, with precise new ways to prevent, diagnose, and treat disease (Jegalian 2000).

(Google “genetics promise medical treatment” and many similarly confident statements can be found.)

Phenylketonuria (PKU) is the poster child for genetic medicine. (The quotes to follow are from Taylor 2014, 131-2.)

> A single measurable genetic factor can be detected at birth by a biochemical test. Severe cognitive impairment can be averted if the appropriate environmental factor—an adhered-to special diet with reduced levels of the amino acid phenylalanine—is present...

Complications

> However, as Paul’s history of PKU screening describes, the certainty of severe cognitive impairment has been replaced by a chronic disease with a new set of problems (Paul 2000, Paul and Brosco 2013, 111ff). For example, although screening of newborns became routine quite rapidly during the 1960s and 70s in the United States, in many states there remains an ongoing struggle to secure health insurance coverage for the expensive special diet. It can be hard to enlist family and peers to support individuals with PKU staying on the diet through adolescence and into adulthood. Math deficits common among individuals with PKU make diet calculations difficult...
>
> Likewise, the apparent simplicity of the genetic factor presumes control over the varying degrees of dietary modification needed by different individuals. Screening has improved over time so that false positives—individuals said to have PKU but needing no special diet—are rare (Sweetman 2001). Yet differences remain among individuals with PKU because hundreds of mutations have been identified in the PAH gene; any individual with PKU may have one pair of mutations out of hundreds of thousands of possible pairs. Efforts are underway to classify mutations as mild, moderate, or severe and as responsive to the drug BH4, which allows a higher-protein diet. Tailoring the dietary modification will require acceptance and application of the diagnostic classification of mutations, secondary screening to place individuals in the right category, and maintenance of the appropriately calibrated diet despite the issues noted in the previous paragraph and some new ones—access to BH4 and keeping individuals who take it from going off the special diet altogether, which is not medically recommended (Paul and Brosco 2013, 108-109). Conversely, when individuals with PKU are not differentiated, this presumes that the medical and health insurance system can withstand any pushback from individuals with PKU or their families about the lack of more personalized treatment.
>
> To acknowledge heterogeneity is not simply to promote more refined genetics-based diagnosis. It can also mean getting involved at a variety of points that shape the PKU life course, such as support groups for individuals and families, campaigns for insurance coverage for the special diet, counseling, or paid family leave. As we consider more recent lines of research on measurable genetic and environmental factors underlying human traits, the case of PKU can serve to remind us to examine the actions possible or proposed on the basis of what is known if one takes into account the possibility of heterogeneity in the genetic and environmental factors.

[Therapeutics & other interventions]

14. Specific genes have effects on psychology that depend on upbringing

(The quotes to follow are from Taylor 2014, 132ff.)

> A 2002 *Science* article reports on antisocial behavior in adults in relation to the activity of monoamine oxidase typeA (MAOA) and childhood maltreatment; MAOA deficiency is a strong predictor of aggressive behavior only when the child has also been maltreated (Caspi et al. 2002).

Complications

> Some meta-analyses have cast doubt on the generality of the Caspi and Moffitt results (Risch et al. 2009; see Morris et al. 2007).

However,

> in order to illustrate the approach and to raise pertinent issues, the discussion that follows uses the 2002 study. The issues raised apply to the overall research program of examining interaction between measured genetic and environmental factors even if these particular 2002-3 results turn out not to be widely replicated.
>
> The authors conclude that their results "could inform the development of future pharmacological treatments" (Caspi et al. 2002, 853). In the context of research on childhood experience in relation to adult behavior, the implication of that conclusion is that, if low MAOA children could be identified, prophylactic drug treatment could reduce their propensity to antisocial behavior as adults. Or, to be more precise, such treatment could reduce their vulnerability, that is, the risk that childhood maltreatment would pave the way to undesired adult outcomes.
>
> An easy rejoinder to the authors' conclusion would be that, if childhood maltreatment could be identified and stopped early, such action could reduce their vulnerability to low MAOA levels paving the way to undesired adult outcomes (Morris et al. 2007). Indeed, eliminating childhood maltreatment would seem to be unconditionally positive, while prophylactic drug treatment may have side effects, some of which may not emerge until later in life. The rejoinder is, however, too easy. Although the intended outcome—eliminating childhood maltreatment—may be seen as positive, the way to get to that outcome might not seem unconditionally positive. After all, detecting and preventing childhood maltreatment might require intrusion into many households, surveillance, monitoring, and intervention by state agencies, diversion of government budgets from other needs, and so on.

Notice that this discussion and the points plotted in figures of the 2002 paper involve

> the averages for the respective categories of people. Within each category people show a range of antisocial behaviors. It turns out that, among children who experienced probable or severe maltreatment, the ranges overlap, that is, some of the high MAOA individuals ended up with higher antisocial behavior scores than some of the low MAOA individuals.
>
> Adjustment of what counts as antisocial does not succeed in eliminating the potential for misclassifying which children are ones who may end up antisocial. If we counted as antisocial only those individuals whose score exceeded some value that is higher than the upper limit of the range for high MAOA individuals, this would increase the numbers of low MAOA individuals who did not end up counting as antisocial. If we lowered the cutoff score, many high MAOA individuals would end up with behavior classified as antisocial...

The issue of misclassification is especially troubling because, once the resources are invested to screen children for MAOA levels, attention would be focused on *all* low MAOA children. Indeed, how could treating children according to their genetic group be avoided if we do not know from a childhood MAOA assessment whether any particular individual is one who would go on, after maltreatment, to become an antisocial adult? Parents might push for additional research to identify other characteristics that differentiate among the low MAOA children and perhaps help predict who among the high MAOA children are also vulnerable. If that research took place and were successful, additional resources would have to be invested to customize the way that parents, teachers, doctors, and social workers treated the different low- and high-MAOA children and to educate everyone not simply to treat children according to which MAOA group they were a member of. In short, the implications of results based on the interaction of genetic and environmental factors depend on what action is proposed once the possibility that heterogeneity underlies those factors is taken into account.

[Variation within & between groups]

15. Personalize medical treatment

(The quotes to follow are from Taylor 2014, 135ff.)

> Personalized medicine in its simplest form, involves the use of genetic information to predict which patients with a given condition (e.g., heart arrhythmia) will benefit from a particular drug treatment (e.g., beta blockers) (Wikipedia N.d.*n*). More ambitiously, personalized medicine promises to inform people of their heightened vulnerability (or resistance) to specific environmental, dietary, therapeutic, and other factors early enough that they can adjust their exposure and risky behaviors accordingly.

Complications

> [T]he path to *personalized medicine* will involve a phase in which large numbers of people are treated *according to their group membership*. Moreover, this phase may not be a passing one.

To appreciate this point, consider an analogy to the MAOA case in the (see Chapter 14):

> [S]uppose the MAOA-maltreatment data concerned not antisocial behavior but a less charged trait, say, a specific adult disease. What kinds of medical diagnoses would receive the necessary investment in pharmaceutical and sociological research, screening, and preventative treatment or monitoring to address the conjunction of genetic and environmental factors involved? One answer is that, especially with the efforts of well-organized parental advocacy groups (Panofsky 2011), government funding might be secured to address the prenatal diagnosis or post-natal treatment of rare debilitating genetic disorders such as PKU. Another answer is that the most likely focus for public and corporate policy would be on diagnoses for which the net benefit, i.e., the number of vulnerable people times the average benefit of ameliorating the effect of the genetic difference, would be large. (More precisely: the focus would be on diagnoses for which the benefit minus the cost of research, screening, and treatment is largest.)
>
> What would the MAOA case lead us to expect for medical diagnoses with large benefit/cost ratios? If the effect of some genetic difference depended on identified social or environmental factors, and if variability within the groups that have, on average, high and low vulnerability produced a problem of misclassification, pressure might arise to differentiate among individuals within the groups.
>
> Until additional research succeeded in identifying distinguishing characteristics, we would expect that parents, teachers, doctors, social workers, insurance companies, policy makers, friends, and the individuals themselves would do the best that they could, which is to use the genetic information to *treat individuals according to their group membership*. If the additional research were not conducted or were not successful, we might never get beyond treatment according to group membership.

[Therapeutics & other interventions]

16. Genomics-based medical system in the near future

> The man of the moment [was] J. Craig Venter, Ph.D., whose pioneering work to sequence the human genome—our essential code for life—had whetted public appetite for medical miracles in the diagnosis, treatment and prevention of even the most complex of common diseases. 'Imagine a world where families leave the hospital with their newborns and take their baby's complete genetic profile with them on a CD-ROM', Venter told his audience. 'And imagine a world where your physician has as part of your medical record your genetic code, which can be used to determine, for example, your risk profile for side effects from drugs or other medical treatments. These might be possible in a genomics-based medical system in the near future' (Massoglia 2003, p. 11).

Complications

(The quotes to follow are from Taylor 2009 438ff)

> 'Imagine a world . . .' If the case of phenylketonuria (PKU) is any guide to our imagination, significant complexities should be expected to arise once neonatal diagnosis and advice about protective measures become widespread. PKU is a condition that many teachers about biology in its social context invoke to demonstrate that genetic does not mean unchangeable. Until the 1960s people with the PKU gene always suffered severe [cognitive impairment], but now the brain damage can be averted through detection of newborns with high levels of the amino acid phenylalanine followed by a special phenylalanine-free diet. Yet, as Diane Paul's (1998 [Paul 2000, Paul and Brosco 2013, 111ff)]) history of PKU screening describes, the certainty of severe [cognitive impairment] has been replaced by a chronic disease with a new set of problems. Screening of newborns became routine quite rapidly during the 1960s and 1970s, but there remains an ongoing struggle in the USA to secure health insurance coverage for the special diet and to enlist family and peers to support PKU individuals staying on that diet through adolescence and into adulthood. For women who do not maintain the diet well and become pregnant, high levels of phenylalanine adversely affect the development of their non-PKU fetuses. This so-called maternal PKU is a public health concern that did not previously exist. In short, a more complex picture of development in a social environment is needed for anyone to make use of the knowledge that the fate of individuals with the PKU gene is not determined at birth.
>
> As we move towards the imagined world of abundant genetic information, we can anticipate debate about who is responsible/who is to blame if a baby is diagnosed, protective measures are not taken or are not sustained, and the child becomes a retarded adult or mother of a child with maternal PKU. Scientists or interpreters of science who want to contribute to improving the lives of people affected by PKU will need to consider where we are prepared to get involved. Would the best point of engagement be around reduction in. diagnosis of variability in effects of exposure, personal motivation and understanding of people with some mental deficits, support groups for individuals and families, insurance coverage for the special diet and for counseling, paid family leave, or . . .?

[Therapeutics & other interventions]

17. Evolution = change of gene frequencies in populations

Biology textbooks usually define evolution as a change of *gene* frequencies in populations over time. If evolution were defined as a change in the frequency of some observed *trait* over time, that change might be related to changes in environmental conditions and could be reversed if those conditions revert to earlier levels.

Complications

Evolution could be defined as a change of *trait* frequencies in populations over time, leaving for investigation whether the change is reversible, accompanied by a change of *gene* frequencies, and so on.

Even with a focus on gene frequencies, the cause of the change in frequencies may not be readily associated with genes. Contrary to many popular accounts, the origin of the heritable variation that is required for natural selection to lead to a new adaptation does not need to be a random mutation. Re-assortment of chromosomes through sexual reproduction, which sometimes involves crossing over and recombination, (Wikipedia N.d.*d*) can provide new variants even in the absence of a new gene mutation.

Moreover, existing uniformity in some traits can turn into variation given a change in the environment. Existing variation may be associated with variation in behaviors that open up new environments, in which subsequent evolution takes place.

Models of evolution by natural selection that begin from the definition of evolution as a change of *gene* frequencies in populations over time include parameters, such as the "fitness" of genes or genotypes (pairs of genes at a given place on the paired chromosomes), that are difficult or impossible to estimate. This situation led population geneticist, Richard Lewontin (1974), to remark (quoting here from Taylor 2003, p. 233):

> "What we can measure is by definition uninteresting and what we are interested in is by definition unmeasurable" (1974, p. 23). The problems of relating models of selection to observations become astronomically worse when there are multiple, linked loci (p. 317). He concluded that we could shift our attention to the fitness effects of variation at the level of chromosomes, and such effects could be measured.

[Selection—artificial & natural]

18. Organisms are the survival machines of genes

> They are in you and in me; they created us, body and mind; and their preservation is the ultimate rationale for our existence… Now they go by the name of genes, and we are their survival machines (Dawkins 2016 [1976], p. 25).

In other words, the genes we have are those that gave our ancestors advantage over competitors in survival and reproduction. Any gene that does not give an advantage will die out—will not survive.

Complications

As the Chapter 17 noted, "parameters, such as the 'fitness' of [i.e., the advantage conferred by] genes or genotypes… are difficult or impossible to estimate," even in well-controlled laboratory populations. Is it possible nevertheless that evolution in the wild could operate in a way that, in effect, discriminates among genes on the basis of the advantage each gene gives in survival and reproduction? How would scientists show that this is the case?

Two deep conceptual assumptions underlie the *Selfish Gene* (Dawkins 2016 [1976]) view of life: 1) There is an agent within any apparent agent–the living being does not develop without being directed by something else; 2) There must be some standard external to organisms (in Dawkins's account, omnipotent natural selection) in order for them to know what they should do.

As noted in Taylor (2013b), there is an irony in Dawkins, the outspoken atheist, making and fostering these assumptions, for these are shared with believers of religion. "Putting the two assumptions together: the directing agent within is mirrored by the directions that people as believers or [as] survival machines should follow" (Taylor 2013b, N.p.).

Perhaps there is a third shared assumption: It is OK to base one's account of the world on unobservables (fitness associated with genes or God) if it is hard for you personally to make sense of the world if the unobservable did not exist.

[Selection—artificial & natural]

19. DNA fingerprinting

> Taking and analyzing a cheek swab of the arrestee DNA is, like fingerprinting and photographing, a legitimate police booking procedure that is reasonable under the Fourth Amendment. (Maryland v. King 2013, N.p.)

Complications

I previously explained how this decision endorses discrimination in the real world given that the databases of such DNA do not include everyone and are not a random sample of all social groups (Taylor 2013c). If the frequency of criminals in groups A and B were the same, but the ratio of group A to group B in the database was skewed towards the group A (*), it follows that, if you are a group B criminal, you are less likely to be identified by this DNA database approach than if you are a group A criminal. The ideal of equal under the law would only apply to the criminal's fate *after* being identified. The problem is exacerbated by disproportionate arrests of group A. (* African Americans and the poor are disproportionately represented in existing DNA databases.)

[Therapeutics & other interventions]

20. If it is passed down, there's nothing we can do (could have done)

(The quotes to follow are from Taylor 2014, p. 158.)

> [C]onsider the results of the study of multiple twins while thinking about your own family. Consider a scenario in which the nonidentical twins are much less similar than identical twins, which means that sharing fewer genes makes a big difference (skipping here the technicalities of getting the number—heritability—that quantifies that result...). If this were the case, for whatever trait we are thinking about, e.g., IQ test score, we might say: "There is nothing I could do as a parent to change the outcome for my offspring. I am not to blame for the outcome other than having passed on my genes." If that conclusion seems justified, we might then reason that the same is true for every other family, and thus society as a whole should not try to change what it is doing because it will not make a difference.

Complications

> Now flip that scenario. Suppose that the nonidentical twins are just as similar, so that sharing fewer genes makes little difference. What can we do as a parent to make a difference in IQ test scores? (If our offspring are grown, we might ask what *could we have done,* or what could we advise others to do, or what should be done by society at large?) Our study of twins has not shown us what environmental factors have an effect, so we do not know what to change. Moreover, we have to face the possibility of underlying heterogeneity, so that we cannot expect the factors to be the same from one family to the next [Chapter 3]. We might then just give up on trying to identify those factors.
>
> Notice the asymmetry in these last two paragraphs. Although the possibility of underlying heterogeneity might lead us to give up looking for the relevant environmental factors, it did not lead us to give up on looking for the genetic factors. This is because our reasoning did not lead us to look for those factors at all. We simply concluded that we were not to blame for the outcome in our family and, by extrapolation, society should not try to change what it is doing. This asymmetry should make us suspect that there is a problem in such reasoning in thinking that, because sharing fewer genes makes a big difference, there is nothing a parent can do to change the outcome...

[Development & functioning of organism]

21. Abnormal conditions provides insight about origin of normal conditions

(This chapter is adapted from Taylor 2009.)

Five offspring of a couple in a remote area of Turkey grew up walking quadrupedally on their hands and feet, as portrayed in the popular science documentary *The Family That Walks on All Fours* (Harrison 2006). Among the various angles of research on the siblings was genetic analysis identifying a mutation in a gene on chromosome 17 influencing cerebellum development and the work of certain evolutionary biologists try to link this gene to the evolution of human bipedalism 3 million years ago. Indeed, other deleterious effects of the gene are depicted as reversing the progress in fine motor coordination and intelligence that accompanied human evolution.

Complications

Scientific disputes arise over these interpretations. Moreover, it is also observed that no medical treatment or physical therapy has been available since the children failed to shift from crawling to walking upright. Following the introduction of a simple walking frame, then exercising between parallel bars, the quadrupedal adults learn to walk upright. The quadrupedal condition may have been genetic in origin, but it was the social infrastructure—or lack thereof—made it hardwired. Adjustments to that infrastructure then softened that wiring.

[Development & functioning of organism]

22. Exceptional responders to drug treatment

Sometimes experimental treatments for cancers are effective for only a small number of patients—"exceptional responders." Sequencing of their cancers may reveal a genetic mutation that explains why the drug was effective (Kolata 2014). Future patients can have their cancer genomes analyzed to determine whether an effective drug is known for their profile of mutations.

Complications

- Drug companies discontinue production of the drug because it works for so few.
- "Researchers. see hundreds of mutations in a cancer and none will explain a patient's response to a drug," molecular oncologist quoted in Kolata (2014, N.p.).
- Cancer centers lure patients using the possibility that they are the rare exceptional responders.

[Therapeutics & other interventions]

23. “All cancers are genetic”

“All cancers are genetic,” genetic oncologists might say. If asked to elaborate, they might explain that “all cancers begin when one or more genes in a cell are mutated (changed), creating an abnormal protein or no protein at all” (American Society of Clinical Oncology N.d., N.p.). If asked what that means for relatives, they would note that “only about 5% to 10% of all cancers result directly from gene defects. inherited from a parent” (American Cancer Society N.d., N.p.).

Complications

> Researchers have estimated that as many as 2 in 3 cases of cancer (67 percent) are linked to some type of environmental factor, including use—or abuse—of tobacco, alcohol, and food, as well as exposures to radiation, infectious agents, and substances in the air, water, and soil (National Cancer Institute 2010).

“Most cancers are environmental,” the health activist might say. If asked to elaborate, they might point to researchers who note that “only 5–10% of all cancer cases can be attributed to genetic defects [which means that] the remaining 90–95% have their roots in the environment and lifestyle” (Anand et al. 2008 [Abstract]). The same researchers conclude that “cancer is a preventable disease that requires major lifestyle changes,” while the health activist might question whether exposure to environmental pollutants or carcinogenic viruses is best thought of as a “lifestyle choice” (ibid). (Who is choosing to be susceptible to cervical cancer when politicians and parents oppose HPV vaccination for their pre-teen children?)

[Development & functioning of organism, Diagnosis by genetic type/sequence]

24. Manipulate enzyme levels related to cancer progression

> New research on an enzyme [PAD2] linked to cancer development shows that 37 percent of mice that produce excessive quantities of the enzyme developed skin tumors within four to 12 months of birth, and many of these growths progressed to highly invasive squamous cell carcinoma, a common form of skin cancer (Buckley 2014, N.p.).

This research built on earlier work suggesting

> that PAD2 is found at high concentrations in several tumor types, but it was not known whether these elevated levels of the enzyme were causing cancer or merely a consequence of tumor progression (Buckley 2014, N.p.).

Moreover, because PAD2 levels are high when there is inflammation this research bolsters the idea that inflammation is involved in the development—or at least the progression of cancer. If the results shown in these mice apply to humans as well, then "further studies aimed at using PAD2 inhibitors to block carcinoma progression in humans" may be warranted (Buckley 2014, N.p.).

Complications

Are mice a good model for humans? A 2010 European Union workshop report ended on an optimistic note, even though "many drugs work well in preclinical trials in mice but turn out to be ineffective when used in clinical trials on humans" and "[m]ost mice used in research are rather young, yet many of the diseases that are of greatest interest to researchers (such as cancer and heart disease) are most common among the elderly," and "researchers investigating the genetic aspects of disease need to take environmental factors (e.g. nutrition, infectious diseases, stress and exercise levels) into account" (European Commission Workshop 2010, p. 6) Some longstanding mice researchers are more skeptical — "Researchers in the United States and abroad were drawing the bulk of their conclusions about the nature of human disease—and about Nature itself—from an organism that's as divorced from its natural state as feedlot cattle or oven-stuffer chickens." (Engber 2011, N.p.).

25. Congenital traits

Some traits that one is born with may be associated with external factors during gestation, such as exposure to thalidomide. Researchers may, however, in deciding which traits to investigate to look for genes, choose congenital traits in the knowledge that they have been formed without the social interactions or environmental influences that occur after birth. Indeed, even when congenital traits are associated with external factors during gestation, investigating the epigenetic basis of the trait—the way it involves turning on or off a gene—may be fruitful.

Complications

> In a field initiated by the epidemiologist David Barker at the University of Southampton, a large number of researchers have been studying associations between nutritional deficits during critical periods *in utero* and chronic diseases of later life, including heart disease and diabetes. The integration of fetal origins and subsequent influences now takes place under the label of *life course epidemiology* (Kuh and Ben-Shlomo 2004) [quoted from Taylor 2014, p. 151].
>
> The associations stand out even after allowing for confounding associations between socioeconomic status, low birth weight, and adult diseases. It appears that, through "gestational programming" of biochemical patterns and cell distribution within organs, disease susceptibility can be inborn, yet with origins that are environmental, not genetic (Taylor 2004, p. 337)

[Development & functioning of organism]

26. Powerful tools

It is said that if one has a hammer, everything looks like a nail. But it may also be said that if one has a hammer one finds unexpected uses for the concentrated force it provides (ranging from combining with an awl to make holes in one's belt to creating a means of murder in who-done-it novels). In the same spirit, technologies to identify DNA sequences can be played around with to expose unexpected uses. Initially, the technologies were used to transfer sequences from complex organisms into bacteria. Soon after, researchers were comparing the sequences within species to see how much variation existed in natural populations, determining whether that variation was of recent origin or had been maintained over a longer evolutionary period, tracing relatedness and genealogies of taxa, etc. etc. Over the last decade, biobanks have been funded -- enormous databases of human genetic variation with accompanying information about disease incidence, with the hope of finding associations between genes and diseases.

Complications

"Playing field is not level"

> (Adapted from Taylor 2009, p. 445)
>
> John Frank (2005), Scientific Director of the Institute of Population and Public Health of the Canadian Institutes for Health Research, has ask[ed] what data needs to be collected over the life course of individuals so that researchers in say, thirty years, have the information needed to identify the key risk factors and interactions that account for variation in disease incidence and differential age of onset in a population, and for changing patterns for diseases over time. He assumes that 'diseases and conditions of later life occur in some and not others because of intense interactions between particular genetic constitutions and particular sequence of social and physical environments.' There is, however, an uneven playing field. Genetic samples are cheap to collect and store and need to be collected only once in a lifetime. Environmental exposures vary over time so that 'new samples are needed whenever exposure changes, are difficult to store, and are 'getting costlier (as awareness of chemical/physical/ biological complexity increases).' Some epidemiologists have secured resources to follow small cohorts through time and collect a rich array of data on the individuals (e.g., The Southampton Women's Survey [Inskip et al. 2006]), but the major investments are being made in collecting primarily genetic and disease data for large samples (e.g., the UK Biobank). Epidemiologists such as Frank have warned that analyses of such data will depend on crude estimates of environmental factors and be subject to large errors, uncertainties, and non-replicated findings about genetic influences. In the absence of longituidinal data on environmental exposures, biomedicine has almost no option but to emphasize the effects of genetic factors (but see Davey-Smith and Ebrahim 2007).

[Tool use & development]

27. Mental illness--social causes or social consequences?

(Adapted from Taylor 2014, p. 123.)

> In a longstanding debate in the sociology of mental illness, “social causation” means low socioeconomic status (SES) increases risk of mental illness, while “social selection” means that the mentally ill decline in SES as a consequence of their illness (Hudson 2005). If genes transmitted from parent to offspring increase the chance of mental illness, then the lower SES of mentally ill for both parent and offspring may be a consequence not a cause of the mental illness of both (Kendler and Baker 2007).

Complications

It is difficult methodologically to distinguish the two kinds of pathways in a given data set—how much consequence, how much cause? Indeed, as Figure 27.1 indicates, there are more than two causal links to investigate.

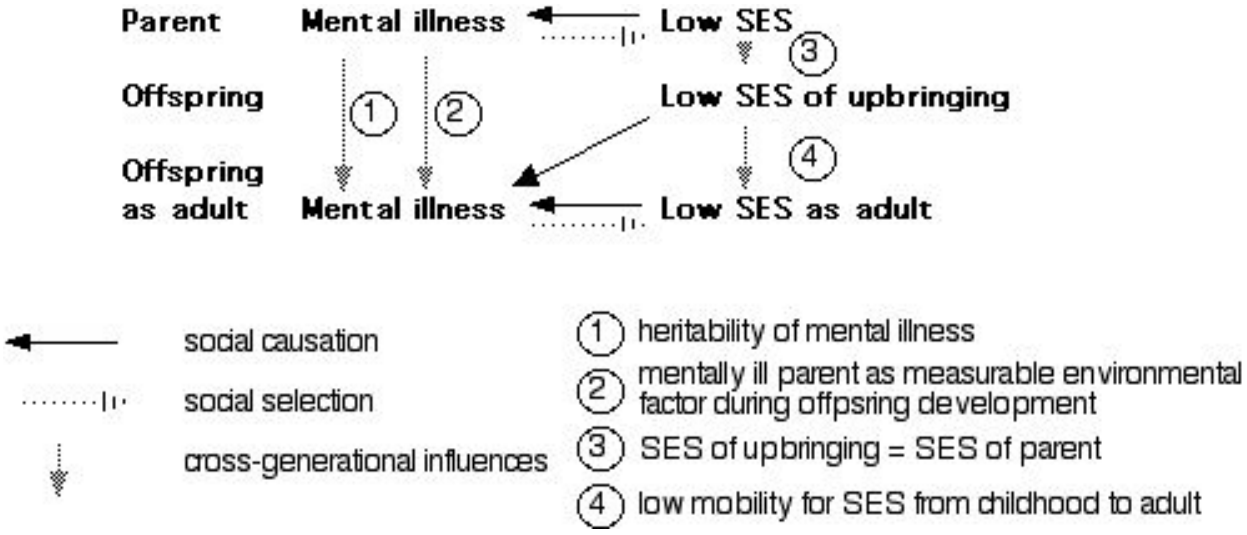


Figure 27.1: Pathways of social causation and social selection for socioeconomic status (SES) and mental illness (Taylor 2014, 123).

Moreover, there is an asymmetry in the contrast: heritability (link 1 in the figure) points to unknown, possibly heterogeneous genetic factors while the environmental factors are measurable and open to intervention (links 2, 3, and 4).

[Variation within & between groups]

28. Genetically-informed social science

(Adapted from Taylor 2014 3, p. 118ff.)

Turkheimer, Emery, and their students have analyzed the similarity of offspring of monozygotic twins with the aim of clarifying the relationship between parental traits, especially divorce, and the behavior of their offspring. Turkheimer (2008, p. 4) describes the logic of their analyses in two scenarios:

> [I]f a genetic propensity to be aggressive makes parents more likely to get divorced, and those same genes when passed to the children make them more likely to be aggressive on the playground, then one will observe an association between divorce and playground aggressiveness that will not really be a causal consequence of divorce….But in identical twin parents…none of the differences between the children can arise from differences in the genes of their twin parent, so if the children do differ, we can (almost…) rule out a genetic explanation of the association.

Conversely,

> Suppose poor families are more likely to be divorced than well-off families, and children raised in poor families are more likely to be delinquent. [We could] observe an association between divorce and delinquency that doesn't have any causal relationship to divorce. But twin parents share their family history of poverty, so if the children of the divorced twin are more likely to be delinquent than the children of the nondivorced twin, the parental poverty isn't a plausible alternative explanation…(ibid).

Turkheimer (2008, p. 5) reports "a rich variability of outcomes"—some indicating a genetic association, some an association with the social factor, and some ruling out hypothesized associations.

Complications

Turkheimer follows up the parenthetical "almost" with caveats concerning, for example, the contribution of the other nontwin parent. Taylor (2014a, 119) lists complications not included among Turkheimer's caveats (complications that are elaborated on earlier in Taylor 2014):

> a) shortcomings in estimation of human heritability, presuming that heritability is what "genetic propensity" refers to;
> b) unreliability of the heuristic that all other things being equal, similarity in traits for relatives is proportional to the fraction shared by the relatives of all the genes that vary in the population;
> c) heritability ("genetic propensity") as a measure of similarity in the trait does not translate in any direct way to hypotheses that invoke underlying genes or genetic factors; and
> d) asymmetry in conceptualization of genetic and environmental (or social) factors—the latter are measurable; the former unknown and potentially heterogeneous.

Taylor (2014, 120-123) continues:

We do not know, however, how much the rich variability of outcomes Turkheimer points to is generated by the unreliable heuristic (issue b. above). Even then, suppose that, for the purposes of discussion, we had results accompanied by an analysis of sensitivity to variation away from the unreliable heuristic value, or even that the heuristic were dispensed with because we had data on the necessary classes of relatives. Could we then interpret similarity or dissimilarity of offspring of monozygotic twins as a "reflection of the environmental and genetic developmental processes that underlie complex human behavior" (Turkheimer 2008, p. 5)?

My answer: Not readily. Turkheimer's phrases "genetic propensity" and "genetic explanation" suggest an equivalence or a direct translation between measures of similarity in the trait and hypotheses that invoke genetic factors underlying the trait, but this is not so. "Genetic explanation," moreover, suggests a symmetry with environmental or social explanation, and this is not so either.

[In this] analysis of the similarity of offspring of monozygotic twins, the environmental factors are measurable and point to interventions, but the genetic factors are unknown, potentially heterogeneous, and informative only for advising close relatives, even in the thought-experiment where issues a. and b. have been overcome.

[Variation within & between groups]

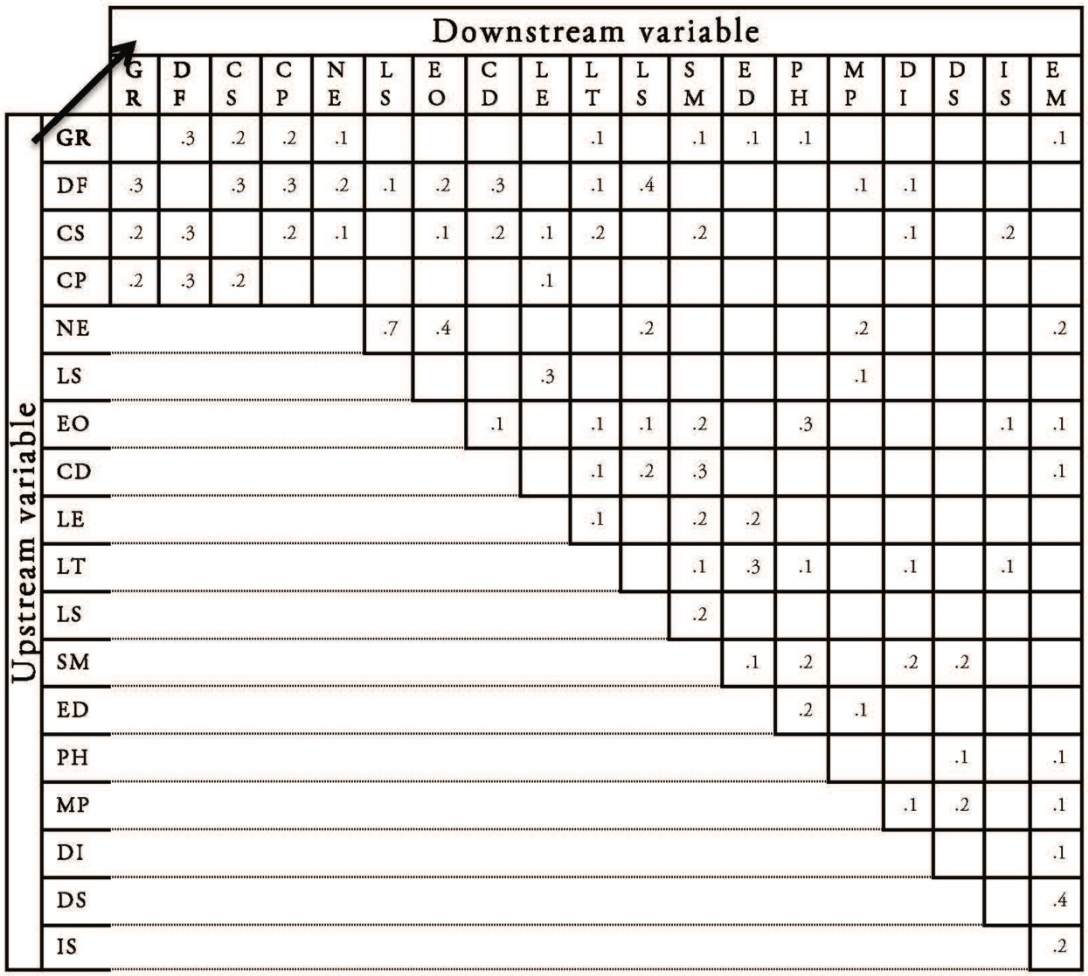
29. Mental illness: Interaction of “genetic risk” with many environmental factors for behavioral traits

(Adapted from Taylor 2014, 137ff.)
Kendler and colleagues examine behavioral traits in relation to a wealth of environmental factors over the life course as well as to the relatedness of the individuals (Kendler and Prescott 2006). In Kendler et al. (2002), for example, data on over 1,900 twins are used to fit the incidence of major depression to an additive model that incorporates many environmental factors and a “genetic risk” factor. This last factor is derived from the incidence of major depression in the co-twin and parents, with adjustments made for the degree of relatedness of the twins (monozygotic versus dizygotic). The model accounts for 52% of the variance in the trait and provides a picture of development that is rich and plausible (see Figure 29.1 below).

Complications
As Kendler et al. (2002, p. 1133) note their “results…should be treated with caution because of problems with causal inference, retrospective recall bias, and the limitations of a purely additive statistical model.”

Another limitation of a purely additive model is that the values of the correlations or path coefficients are dependent on the network of factors chosen by the researchers. For Kendler and colleagues, this dependency might not seem to be a noteworthy limitation, given, as the paper’s title—“towards a comprehensive developmental model”—indicates, a very wide range of factors are taken into account. Moreover, in the initial network every factor is linked to every other factor. The links are then pruned to arrive at a less saturated network, but it is the data analysis that indicates which links in the network have low correlations or path coefficients. Finally, before arriving at the final published network, the researchers examine whether the degree of fit of the model to the data is sensitive to the inclusion or omission of factors. These virtues notwithstanding, the results remain dependent on the network of factors chosen by the researchers. The research of Kendler et al. (2002) does not include factors that correspond to therapeutic interventions or to social changes that have led to the rising incidence of depression. (Kendler [pers. comm., 2005] explains that their research is intended to be basic, not applied, science.

Model for Predicting an Episode of Major depression*



* Adapted from Kendler et al. (2002). The numbers represent the correlation or path coefficient between the variables: GR, genetic risk for major depression; DF, disturbed family environment; CS, childhood sexual abuse; CP, childhood parental loss; NE, neuroticism; LS, low self-esteem; EO, early-onset anxiety; CD, conduct disorder; LE, low education; LT, lifetime trauma; LS, low social support; SM, substance misuse; ED, ever divorced; PH, past history of major depression; MP, marital problems in last year; DI, difficulties in last year; DS, dependent stressful life events in last year; IS, independent stressful life events in last year; EM, episode of major depression in last year. See text and original source for further explanation.

Figure 29.1 Model for predicting an episode of major depression. Source: Taylor (2014, 138). Adapted from Kendler et al. (2002).

[Variation within & between groups]

30. Genetic heterogeneity

Genetic heterogeneity refers to

> either: a) a multiplicity of mutations within some gene and a spectrum of corresponding values for a trait (or "phenotype"), each of which varies little within the typical range of locations (i.e., *allelic* heterogeneity); or b) the trait exists if any one of a range of loci has the atypical form (i.e., *locus* heterogeneity) (Taylor 2014, p. 93).

For example, in the case of phenylketonuria (PKU)

> differences remain among individuals with PKU because hundreds of mutations have been identified in the PAH gene; any individual with PKU may have one pair of mutations out of hundreds of thousands of possible pairs. Efforts are underway to classify mutations as mild, moderate, or severe and as responsive to the drug BH4, which allows a higher-protein diet. Tailoring the dietary modification will require acceptance and application of the diagnostic classification of mutations, secondary screening to place individuals in the right category, and maintenance of the appropriately calibrated diet despite the issues noted in the previous paragraph and some new ones—access to BH4 and keeping individuals who take it from going off the special diet altogether, which is not medically recommended (Paul and Brosco 2013, 108-109) (Taylor 2014, 131-2).

Complications

The complications are evident already above, as researchers look to make the distinctions between different variants of the PAH gene and medicine bases its actions on the resulting knowledge. Complementary complications arise from treating people with a mutation in a gene, e.g., PAH, as if they had the same condition.

[Diagnosis by genetic type/sequence]

31. Root causes

Human behaviors, diseases, and treatments obviously all involved actions taken in a social context, but, given that everyone is made up of cells and all of one's cells operate under instructions from one's inherited and more or less unchanging genome, looking for genes is a way to look for root causes—causes on which to build our understanding and any corresponding interventions.

Complications

The unchangeability of the inherited genes—the root causes—says nothing about the most effective, economical, or otherwise socially desirable intervention (or combinations of interventions) to pursue. To illustrate this for my students, I use the following stylized example (Taylor 1995).

A body of research, initiated by the British sociologists Brown and Harris in the 1960s, has interpreted the social origins of mental illnesses. Let me sketch their explanation of acute depression in working-class women in London (Brown and Harris 1978, 1989). I will also work in the extensions of their findings made by Bowlby, a psychologist who focused on the long term effects of different patterns of attachment of infants and young children to their mothers (Bowlby 1988).

Four factors are identified by Brown and Harris as disproportionately true of women with severe depression: a severe, adverse event in the year prior to the onset of depression; the lack of a supportive partner; persistently difficult living conditions; and the loss of, or prolonged separation from, the mother when the woman was a child (under the age of eleven). Bowlby interprets this last factor in terms of his and others' observations of secure versus anxious attachment of infants and young children to caregivers. In a situation of secure attachment the caregiver, usually the mother, is, in the child's early years, "readily available, sensitive to her child's signals, and lovingly responsive when [the child] seeks protection and/or comfort and/or assistance" (Bowlby 1988, p. 167). The child more boldly explores the world, confident that support when needed will be available from others. Anxious attachment, on the other hand, corresponds to inconsistency in, or lack of, supportive responses. The child is anxious in its explorations of the world, which can, in turn, evoke erratic responses from caregivers, and the subsequent attempt by the child to get by without the support of others.

The top three strands of the figure above (class, family, psychology) combine the observations above to explain the onset of serious depression. The factors are not separate contributing causes, like spokes on a wheel, but take their place in the multi-stranded life course of the individual. Each line should be interpreted as one contributing causal link in the development of the behavior. The lines are dashed, however, to moderate any implied determinism; the links, while common, do not apply to all women at all times, and are contingent on background conditions not shown in the diagram. For example, in a society in which women are expected to be the primary caregivers for children (a background condition), the loss

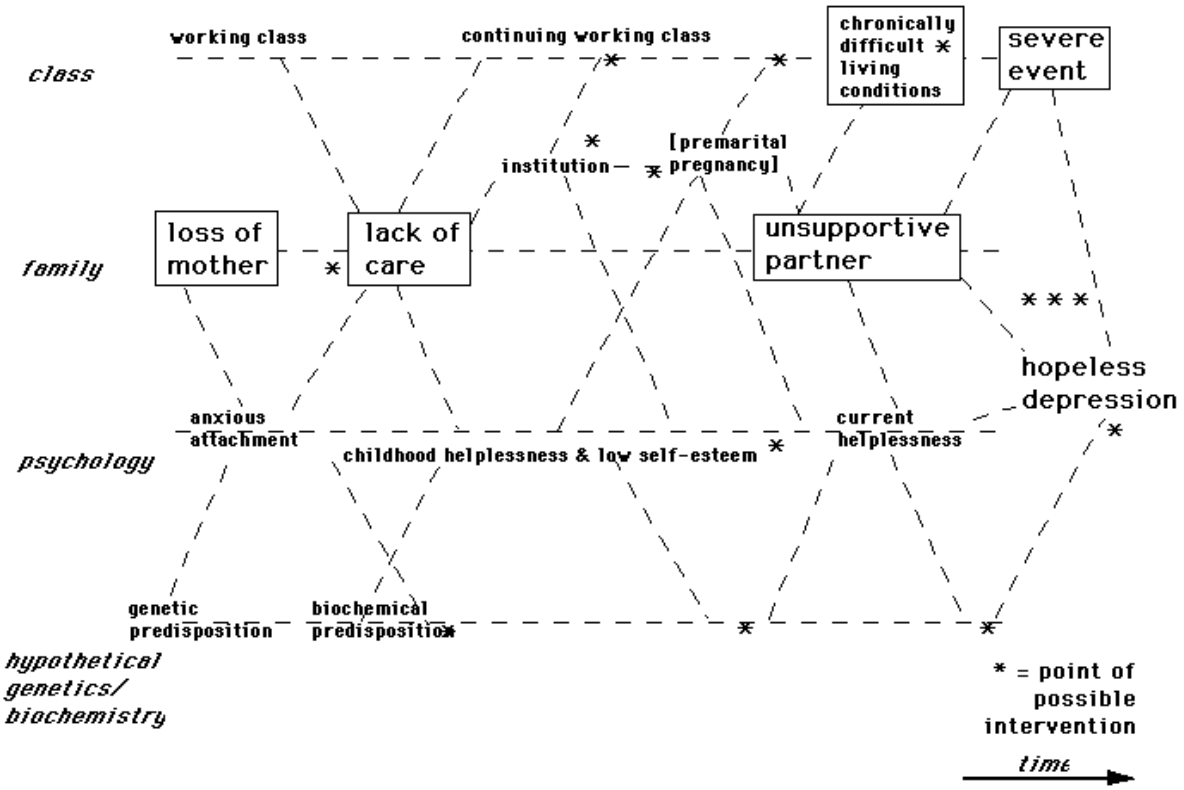


Figure 31.1. Life-course origins of clinical depression in study by Brown and Harris (1978) as elaborated by Bowlby (1988) and author. (Source: Taylor 1995)

of a mother increases the chances of, or is linked to, the child's lacking consistent, reliable support for at least some period. Given the dominance of men over women and the social ideal of a heterosexual nuclear family, an adolescent girl in a disrupted family or custodial institution would be likely to see a marriage or partnership with a man as a positive alternative, even though early marriages tend to break up more easily. In a society of restricted class mobility, working-class origins tend to lead to working-class adulthood, in which living conditions are more difficult, especially if a woman has children to look after and provide for on her own. In many such ways these family, class, and psychological strands of the woman's life build on each other.

Suppose now, quite hypothetically, that certain genes, expressed in the body's chemistry, predispose a child to being more anxious in attachment compared to other children, even those within the same family. Suppose also that this inborn biochemistry (or the subsequent biochemical changes corresponding to the anxiety) renders the child more susceptible to the biochemical shifts that are associated with depression. (This hypothetical situation is depicted in the bottom strand of the figure.) It is conceivable that early genetic or biochemical diagnosis followed by lifelong treatment with prophylactic antidepressants could reduce the chances of onset of severe depression. This might be true without any other action to ameliorate the effects of loss of mother, working-class living conditions, and so on. There are, however, many other readily conceivable interventions to reduce the chances of onset of depression, for example,

counseling adolescent girls with low self-esteem, quickly acting to ensure a reliable caregiver when a mother dies or is hospitalized, making custodial institutions or foster care arrangements more humane, increasing the availability of contraceptives for adolescents, increasing state support for single mothers, and so on. If the goal is reduction in the incidence of severe depression for working-class women, the unchangeability of the hypothetical inherited genes says nothing about the most effective, economical, or otherwise socially desirable intervention (or combinations of interventions) to pursue.

[Therapeutics & other interventions]

32. Production of usable amounts of medicinal biochemicals

From the early 1960s researchers looked for the hormones—that controlled white blood cell production. By the early 1980s, having identified and purified the chemicals—Colony Stimulating Factors (CSFs), the problem was to extract enough pure CSFs from tissues to use clinically.

> "To get enough material for one patient we would have had to work for 250 years," Professor Metcalf [of the Walter and Eliza Hall Institute] said. "We had purified CSF, we had done elegant tissue culture experiments, but now we're into logistics and were facing a big black hole." The team decided to try to use genetic cloning to produce CSFs for use in the lab. [By] 1986, they (and other groups) had cloned all four CSF genes from the mouse and human genomes, and had started producing them *en masse*. After 20 years of research, the hormone was finally ready to trial in animals. And it worked. [By 2009] more than 20 million cancer patients ha[d] benefited from the therapy (Walter and Eliza Hall Institute 2012).

Complications

1.

> Acute myelogenous leukemia (AML) is a fatal bone marrow cancer. Colony-stimulating factors (CSFs) are frequently administered during and after chemotherapy to reduce complications… [But CSFs] should not be given routinely to acute myelogenous leukemia patients post-chemotherapy since they do not affect overall survival or infectious parameters including the rate of bacteremias and invasive fungal infections (Gurion et al. 2012, 1, 26).

2. Cost-effectiveness. CSFs are not cheap to provide so studies are undertaken to estimate the cost-effectiveness of CSF use in, for example, early-stage breast cancer when its use is directed to those most in need of the medication. The relevance of defining "populations for which therapy is, or is not, cost-effective" (Silber et al. 1998, 2435) depends on national healthcare budget and policies (e.g., universal insurance) and an individual's coverage.

[Production, Therapeutics & other interventions, Tool use & development]

33. Advice to relatives

As noted in Chapter 3, high heritability might mean that the similarity between twins or a set of close relatives is associated with the similarity of yet-to-be-identified genetic factors [but] *the factors may not be the same from one set of relatives to the next, or from one environment to the next*. This is one reason why translation from estimation of heritability to hypotheses about measurable factors is difficult. One response to this situation is to

> [r]estrict attention to variation *within a set of relatives*. Even if the underlying factors are not yet known, high heritability still means that if one twin develops a trait (e.g., type 1 diabetes), the other twin is more likely to as well. This information might stimulate the second twin to take measures to reduce the health impact if and when the disease starts to appear (Taylor 2014, p. 31).

Complications

> [N]otice that this path assumes that the timing of getting the condition differs from the first twin to the second. Researchers might well then ask: What factors influence the timing? How changeable are these? How much reduction in risk comes from changing them? To address these issues researchers would have to identify the genetic and environmental factors that influence the development of the trait. To do so would require larger sample sizes than any single set of relatives allows. The question then arises whether the initial results would carry over from one set of relatives to others. This issue is an empirical one; there is a risk. that the proportion of fruitful investigations will be low compared to those confounded by factors not carrying over well from the initial set of relatives (Taylor 2014, p.31).

Additional complications follow from asking what to do about the possibility of underlying heterogeneity of the genetic and environmental factors.

Moreover, this advice to relatives does not depend on looking for, or finding, the genes. (Including this chapter in this series of posts runs the risk of bolstering the idea that heritability, which comes from analysis of traits, has something to do with whether a trait is heritable in the sense of caused by genes transmitted from parents to offspring.)

[Therapeutics & other interventions, Variation within & between groups]

34. Physiologists' approach to plant improvement

(The quotes to follow are from Taylor 2014, 101ff.)

There is

> a longstanding tension within agricultural research between, broadly speaking, *breeders* and *physiologists*. Breeders seek improvement through selection of varieties combined with plant or animal husbandry appropriate to those varieties. Physiologists focus on determining and manipulating the specific genetic and environmental factors underlying the development of the trait in question. (In this era of genomics, breeders may also be physiologists, but let [us] continue distinguishing the two ideal types.) Breeders are not uninterested in the underlying factors. They make hypotheses about such factors based on trials [of multiple varieties grown in multiple locations] as well as sources other than the data analysis, then use these hypotheses to plan the next set of varieties and locations on which to collect data. Physiologists make much less use of variety-location trials to generate hypotheses; instead they focus on experiments under controlled conditions. Since the advent of DNA technologies, their experiments have included modification of specific genetic factors.

Complications

> The question that arises is whether the factors that are important under the controlled conditions also apply more broadly...? If not, the controlled conditions have to be prescribed and replicated in actual plant or animal husbandry. The breeder is not so constrained. Even in the absence of realistic models of the underlying factors and even if those factors are heterogeneous, it is sometimes possible that progress through selection and mating can be made. Breeders can compensate for any less-than-expected progress from one generation to the next by continuing selective breeding for more generations. Physiologists. want to design experiments around genetic and environmental factors that are likely to be important influences on the trait being studied...

How does this breeder-physiologist tension play out for human heritability studies? After all, controlled mating and selection is not possible, nor are trials based on each of a set of varieties raised in each of a set of locations. On the physiologist side, there are obviously serious limits to the use of experiments to determine and manipulate the specific genetic and environmental factors underlying the development of human traits.

[Development & functioning of organism, Selection—artificial & natural]

35. Find “missing heritability”

From Taylor (2014, p. 124):

> [G]enomic studies have had difficulty identifying causally relevant genetic variants behind variation in human traits (McCarthy et al. 2008, Couzin-Frankel 2010). Even when many genetic variants are examined together, only a small fraction of the variation in the trait is associated with—or in statistical terms, “accounted for” by—the genetic variants. This finding has led to discussions about *missing heritability* (e.g., Manolio et al. 2009)...

and bridging the gap by finding additional genetic variants (e.g., Wheeler and Barroso 2012).

Complications

The expectation that genetic variants could account for a larger fraction of trait variation follows from ambiguous descriptions of heritability as. the “fraction of the variance of a phenotypic trait in a given population caused by (or attributable to) genetic differences” (Layzer 1974, p. 1259). However, the heritability of classical heritability studies (which is Layzer’s focus) *has no empirical or conceptual relationship* to assessing the fraction of the variation in the trait is associated with—or in statistical terms, “accounted for” by—the genetic variants (see Taylor (2011b), “Heritability, a technical term, can be visualized by non-specialists” (N.p.)). Researchers are free to search for additional genetic variants associated with a disease, but there is no missing heritability that provides a warrant for their work.

[Variation within & between groups]

36. Ancestry might have medical significance

BRCA1 and *BRCA2* mutations are more common in certain populations (e.g., people of Ashkenazi Jewish descent) than others. Closer monitoring or prophylactic measures might be undertaken following positive tests (by genomic sequencing) for those mutations. Genomic studies are identifying other genetic variants of biomedical significance that are more common in people of specific regions and thus of people whose ancestry traces to those regions (e.g., Genovese et al. 2010). Even if no preventative measures are available, the tested individual and their doctors can more accurately assess risk for the particular biomedical condition once testing has been done. (For example, instead of saying ”breast cancer risk is slightly higher among Jewish women than among other women” (Susan G. Komen N.d., N.p.) presumably because of higher prevalence of BRCA1 and BRCA2 mutations, one can say to a woman of Ashkenazi Jewish descent that your risk is xx given that you do not have those mutations [where xx depends on age and family history].)

Complications

1. If preventative measures come with a cost, e.g., prophylactic ovary removal (oophorectomy), how does one give weight to the higher, but no means 100% risk? The “regret factor” (i.e., what will I feel like if I didn’t take prophylactic action and I end up with cancer) can make risk into a black or white matter.

2. If monitoring comes with a cost, decisions get made about when the cost outweighs the benefit or, when the screening is done anyway, that may come at the cost fewer medical or public health resources being available for other modes of prevention (see Taylor (2010) on reactions to proposed changes in mammogram guidelines).

3. Because genetic testing is expensive, perceived race/ethnicity can be used as a proxy for possession of the genetic factor and thus shape treatment. Consider the following scenario:
Suppose you are a doctor seeing a patient with hypertension. The patient is a 54 year-old black man. What should you do? What more do you want to know before deciding what to do?

Perhaps you already know more along the following lines:

> Regardless of region, blacks were less likely than whites to achieve treatment success with atenolol (P = .02) or prazosin (P = .03) and more likely with diltiazem (P = .05). (Cushman et al., 2000, N.p.)

(Atenolol is a beta blocker; prazosin lowers blood pressure by relaxing blood vessels; diltiazem is a calcium channel blocker).

You might say to yourself, “I know that not all black men with hypertension do better with calcium channel

blocker and worse with beta blockers, but on average they do. So I'll prescribe diltiazem and see what happens. If it doesn't work well, I'll change the medication."

Complications in this scenario are teased out in Taylor (2011c).

[Origin by descent, Therapeutics & other interventions]

37. Customize treatment of tumors

Cancer tumors exhibit an accumulation of mutations in DNA (something distinct from inheriting a mutation that increases one's likelihood of getting a given type of cancer (Chapter 23)). This results in tumors having particular genetic profiles in different people even if the people are diagnosed as having the "same" cancer. Sometimes the effectiveness of a treatment can be predicted according to the genetic profile of the tumor. Clinical researchers are gathering data in the hope of classifying the genetic profiles into groups in relationship to their response to available treatment options.

Complications

1. The genetic profile of a tumor changes as the disease progresses.

2. The heterogeneity of the genetic profiles of tumors might not allow clear grouping or not into groups related to response to available treatment options. (Consider, as relevant analogies: a. genetic heterogeneity in single-locus diseases, such as PKU (Chapter 30); and b. the difficulty that "genomic studies have had. identifying causally relevant genetic variants behind variation in human traits. Even when many genetic variants are examined together, only a small fraction of the variation in the trait is associated with—or in statistical terms, "accounted for" by—the genetic variants [Taylor 2014, p. 124].)

3. Customized treatment, although often described as personalized cancer therapy or precision medicine (UC San Diego Health N.d.), "involve[s...] people [being] treated *according to their group membership*. Moreover, this phase may not be a passing one (Taylor 2014, pp.135ff; see Chapter 15).

[Diagnosis by genetic type/sequence, Therapeutics & other interventions]

38. Select sex of the baby

Prenatal tests can determine the chromosomal sex of the fetus as early as 10 weeks into the pregnancy. If the fetus is not of the desired sex, it can be aborted.

Complications

1. Selecting the sex of the baby happens by rejecting the fetuses that are not of that sex.

2. That selective abortion by sex is happening even when illegal is evident, for example, in the sex ratio of second children in India. The parents take their chances the first time, but, if they have a girl, enough parents resort to sex-selective abortion that the sex ratio of second children is skewed towards male babies (Manchanda et al. 2011).

3. The social implications of this imbalance could be significant, if that is not the case already (e.g., Hesketh and Min 2012, Lee 2011).

[Diagnosis by genetic type/sequence, Therapeutics & other interventions]

39. Assign humans to groups that arose after dispersal from Africa

Population geneticist, Richard Lewontin "found that the majority of the total genetic variation between humans (i.e., of the 0.1% of DNA that varies between individuals), 85.4%, is found within populations, 8.3% of the variation is found between populations within a 'race', and only 6.3% was found to account for the racial classification. Numerous later studies have confirmed his findings" (Wikipedia, N.d.*i*). Critics of Lewontin, including philosopher Sesardic (2010), have observed that the fact that variation within a group is of larger than variation between (the average of) the groups, does not mean that the groups cannot be distinguished. (The quotes to follow are adapted from Taylor 2011a, 469ff.)

> Let me affirm this last point with an example from a course I once took in multivariate statistics. We could not say with confidence whether a student was male and female on the basis of their height—there was too much overlap of the ranges—or, for the same reason, on the basis of their hip circumference. Yet a simple linear function that subtracted hip from height was very reliable in discriminating male from female students. In Sesardic´s figure, rotated 90 degrees below, height would be the x-axis, hip the y-axis; the squares the males, the triangles the females.

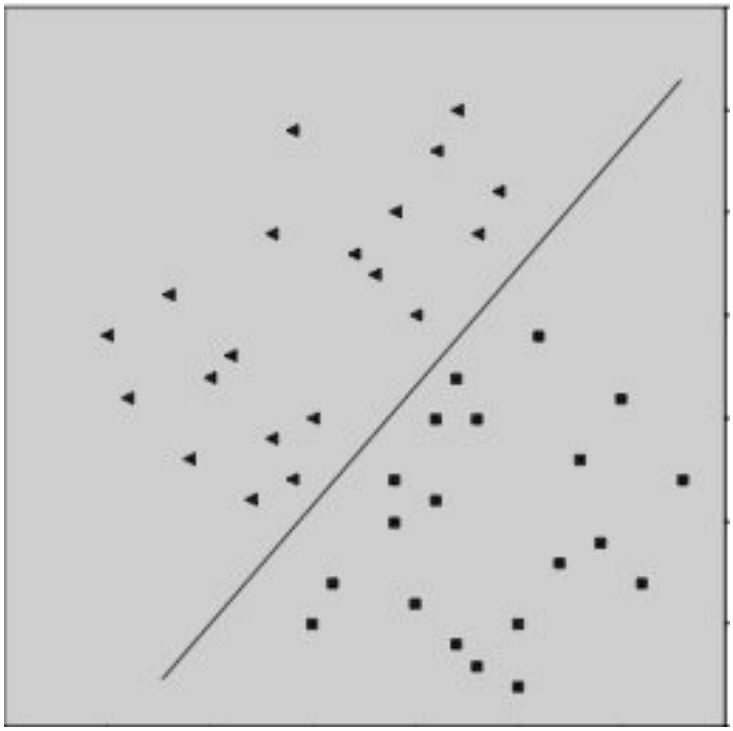


Figure 39.1: Distinguishing groups for which there is a lot of within-group variation relative to the difference in their average values (adapted from Sesardic 2010 in Taylor 2011a)

Complications

This point is not, however, sufficient to rehabilitate a biological picture of race.

> Suppose we imagine an original human gene pool that dispersed at some point of time from its origins in Africa around the world and was *not* subject to subsequent breeding among widely dispersed parts of the pool. Cluster analysis techniques could be used on

> genetic data to divide humans into, say, N groups. Such clustering techniques are sensitive to assumptions that determine whether groups are of roughly equal size or are a mix of a few large groups. If we looked for groups that had similar within-group genetic variation, most of the N groups would be in Africa. In other words, the traditional subdivisions of human races would have to be reformulated.

Of course

> there has been considerable migration and cross-breeding subsequent to the initial dispersal from the place of human origin in Africa, including but not confined to the recent centuries of cross-Atlantic slavery and master-slave relations. How well could we recover from current individuals the one or more groups (as delineated [above]) that make up the individuals´ ancestry? [T]his is an empirical question. Biomedical researchers [might well] judge that research efforts might be more fruitfully directed along other avenues, such as those indicated by biomedical correlates of socially defined race (i.e., not the groups that would emerge from the cluster analyses....

Even if we were to put aside the issues above and

> imagine a world in which we were able to use genetic information to assign humans to original post-dispersal groups as reliably as in the statistics class we were able to assign individuals to male and female groups. What could we do with that knowledge that there is a difference between the average genetic profiles for groups A and B when there is large within-group variation for most genetic loci (at least, for those that vary within the human species)?
>
> Let me accentuate this question with using the IQ test score case Sesardic has paid considerable attention to (2005). Suppose we knew (which we do not) that only a certain small set of genes influenced IQ test scores. What could we do with the knowledge that there is a large difference between the average IQ test score for two groups and this difference is smaller than the within-group variation? (To visualize this situation, imagine one of the axes in the Figure is IQ test score.) [Who would use the] ability to assign humans to original post-dispersal groups based on genetic profiles as grounds for using an individual´s membership in a group to make educational or employment decisions for the individual?

[Origin by descent]

40. Determine one's ancestry

Examining a male's Y chromosome can expose genetic variants (or a pattern of variants) common in certain regions of the world and thus tell you that the root of his ancestry going through father-paternal grandfather-etc. probably originated in that place. Similarly, examining a female's X mitochondrial DNA, which are transmitted from the egg and not the sperm, can tell her the root of her ancestry going through mother-maternal grandmother-etc. probably originated in a given place.

Each of us has, of course, many, many more ancestral roots than these two. "Ancestry-informative markers"—variations at specific places on the genome that differ between regions, can be used to estimate proportions of one's ancestry that originated in various different regions (Wikipedia N.d.*a*).

Complications

1. "Passed through" would be more accurate than "originated," given that all *Homo sapiens sapiens* trace back to one woman, who lived in Africa between 100,000 and 200,000 years ago (Wikipedia N.d.*k*). Similarly, all Homo sapiens males trace back to one man, who lived in Africa between 140,000 and 330,000 years ago (Wikipedia N.d.*s*). (Many people also have a fraction of their genome from *Homo neanderthalensis*.) So one needs to set some arbitrary point in the past for determining the region of one's ancestors.

2. "Common in certain regions of the world" means common today. The ancestors of people living in some region today need not have lived in that region at the particular point in the past chosen for determination ancestry.

3. Knowing the proportion of one's ancestry that originated in a particular region does not imply that you possess a corresponding proportion of the genes that are common in that region. The reason: At any time, in any region there is great variation among individuals in their genetic make-up (see Chapter 39). Indeed, it is difficult to "depict genetic relationships among humans in ways that allow simultaneously for similarity, diversity, and admixture at the same time as we depict ancestry" (Taylor 2011d, N.p.).

[Origin by descent]

41. Depict the Tree of Life

The Tree of Life denotes a range of images or mythologies about the interconnectedness or unity of all things; also, sometimes their fruitfulness (Wikipedia N.d.*r*). One form of interconnectedness or unity is the sharing of a common ancestor, which can be seen in the branching diagrams of phylogeny (i.e., evolutionary branching) or classification of taxonomic groups (Tree of Life Web Project N.d.). In molecular systematics, phylogenies are derived from differences in DNA sequences combined with assumptions about uniform rates of mutation in those sequences, especially in the third base pair of a coding triplet (where differences have little influence over the function of the resulting protein).

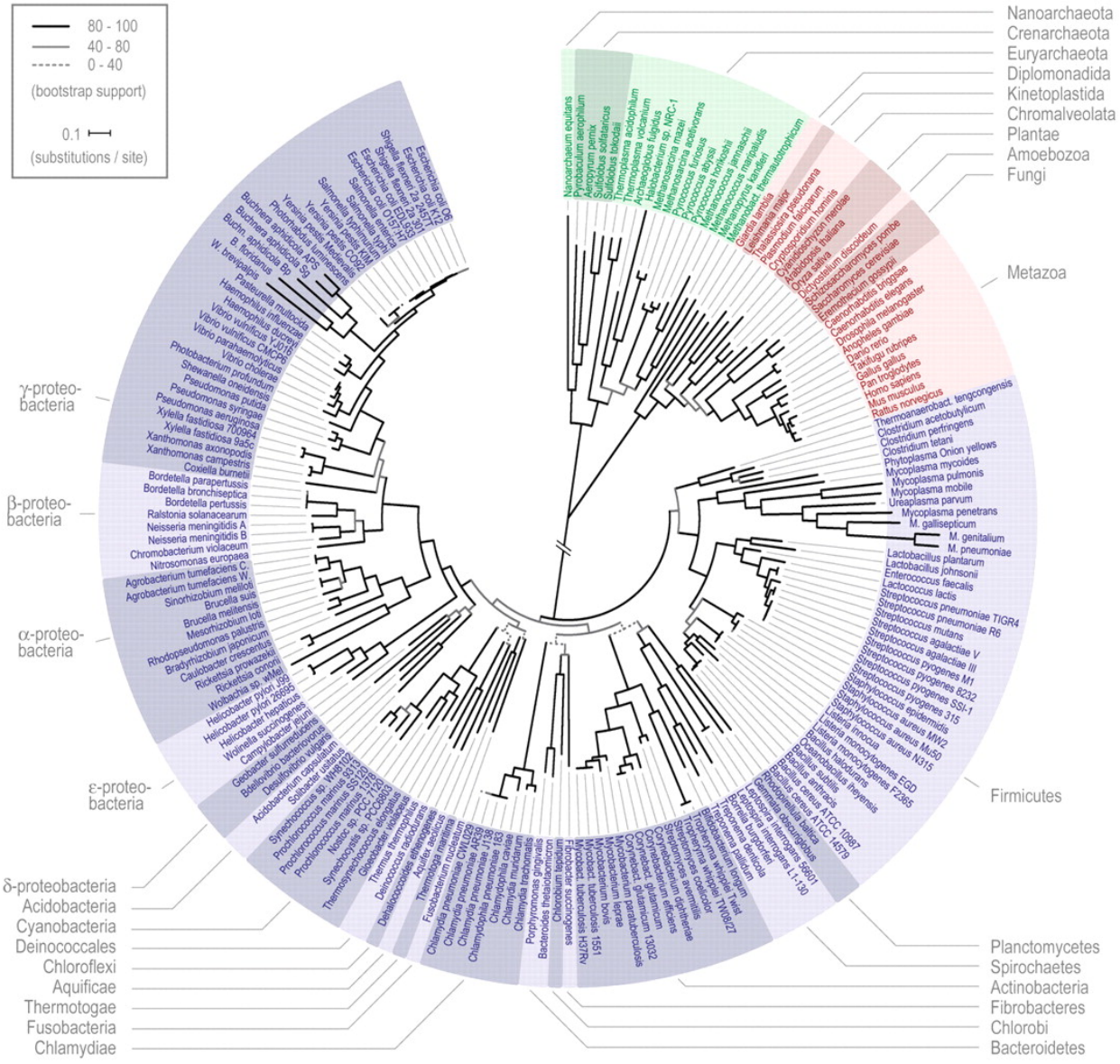


Figure 41.1: Global phylogeny of fully sequenced organisms (Source: Ciccarelli et al. 2006)

In the course of constructing these phylogenies, researchers have learned that organisms as dissimilar as humans and rice share a significant fraction of genes—25% for humans and rice (Zimmer 2013).

Complications

1. The fraction of genes shared was, when first discovered, interpreted as if the traits were conserved across the diverging branches of the tree or seen as a puzzle, given that some of the genes were involved in traits that did not even exist in the distant common ancestor of the organisms.

2. Soon, however, it was recognized that "[t]he genes we still share we use differently, in the same way you can use a clarinet to play the music of Mozart or Benny Goodman" (Zimmer 2013, p. 102). (Perhaps using a cello to play Bach versus harmonic singing might be a better analogy (Hopkins 2011)).

3. Once it is recognized that genes can have different functions in distant lineages, the question arises as to how close the lineages have to be (i.e., how recent the common ancestor) before the function can be treated as the same. In that spirit, for example, although chimpanzees and bonobos differ from humans in 1.2% of the genome, it does not necessarily follow that the other 98.8% is doing the same thing in the two groups.

4. The phylogenies produced using molecular data vary according to assumptions made and do not readily allow for horizontal gene transfer among distinct lineages (Wikipedia N.D.*l*).

[Origin by descent]

42. Depict human genealogical and genetic relationships

Using genome-wide variation it is possible to depict the variation among humans in ways that indicate the divergence from a common ancestral group. The following diagram comes from the work of Campbell and Tishkoff (2010) on genetic variation among humans in and out of Africa.

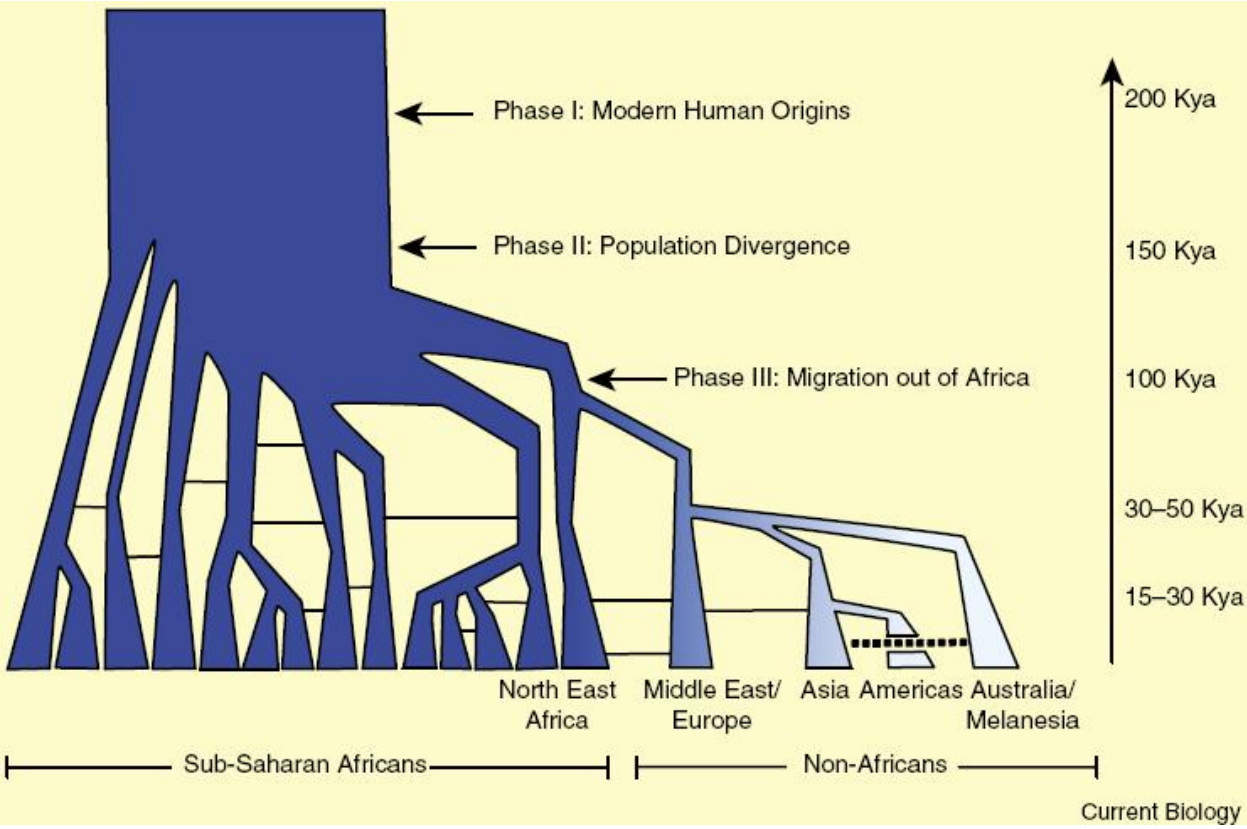


Figure 42.1: The Recent African Origin model of modern humans and population substructure in Africa. (Source: Campbell and Tishkoff 2010)

The diagram shows that there are many more branches leading from the ancestral within-Africa human population to current African groups than there are to groups in the rest of the world, that is, to groups derived from people who migrated out of Africa at some point after 100,000 years ago. This branching pattern suggests that, if we were to divide human genetic diversity into a small number of groups of similar diversity, say, five groups, then most of these groups would be African. (Indeed, four would be from Africa and the fifth would be a combination of an East African group and the non-African groups.). This finding seems to discredit the genetic reality of traditional races, where “traditional” has varied greatly but in general separates Africans, Asian, Australian, and Europeans or “Caucasians.”

Complications

1. The diagram places the non-Africans out on the right, taking up 40% of the horizontal scale, and

colored lighter, all suggesting that the rest of the groups can still be lumped together. Would someone who promotes (or promoted) a traditional racial classification would be at all troubled by learning that their African race was really a collection of 13-14 races? If they had the idea that something special genetically happened in the branch that left Africa, then those groups left in Africa are united in *lacking* that something.

2. Can any depiction of genetic relationships among humans allow simultaneously for similarity, diversity, ancestry, and admixture (i.e., groups that had split mixing again)?

3. Our familiarity with phylogenetic trees invites us to think—even if subconsciously—about human genetic ancestry as if the branches are like separate species (Chapter 41). This resonates with a long history of scientific arguments that human races are separate species, or that the branches of the human tree achieved human status at different rates. We might ask, therefore, whether the very methodology of generating and depicting human ancestry privileges a racialized view of human diversity?

This post is adapted from the first of a series of previous posts exploring depictions of human genetic relationships (Taylor 2011d).

[Origin by descent, Variation within & between groups]

43. Runs in families

Patterns of occurrence of a disease in a family pedigree or genealogy can suggest transmission of a mutation closely related to that trait. Hemophilia in male descendants of Queen Victoria is a classic case, in which female descendants can be carriers of the mutation. (see Figure 43.1)

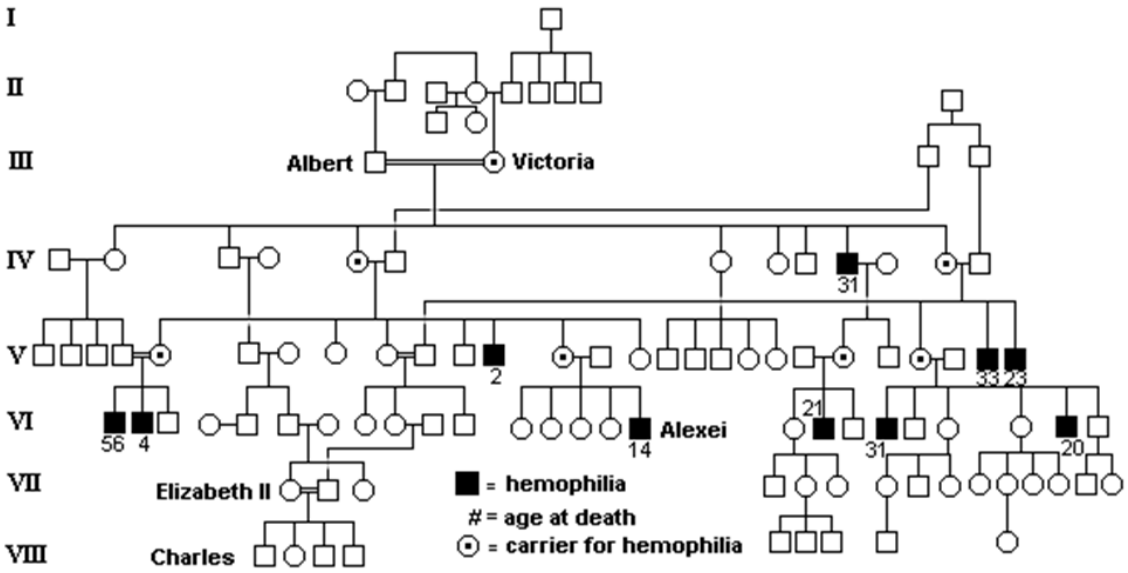


Figure 43.1 Pedigree Diagram for Royal families of Europe (Source: http://bit.ly/rfhemophilia)

Complications

During the heyday of eugenics in the early C20, the same method was used to suggest transmission of genes related to much less specific traits, such as, intellectual renown in the Darwin-Wedgewood-Galton family tree (Figure 43.2).

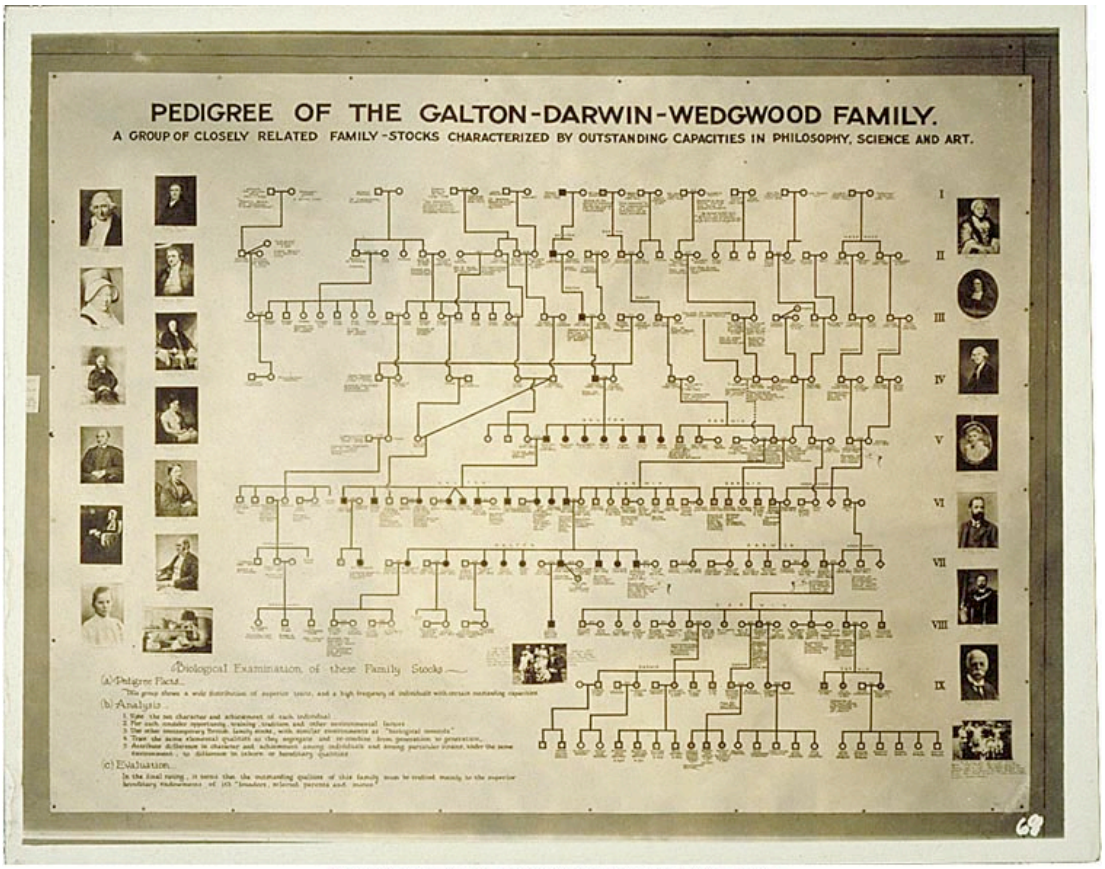


Figure 43.2: Pedigree of the Darwin-Wedgewood-Galton Family. (Source: Cold Spring Harbor Laboratory Image Archive, http://bit.ly/darwinwedgewood)

Or feeble-mindedness in the Kallikak family, the subject of a 1912 book by H. Goddard (Figure 43.3).

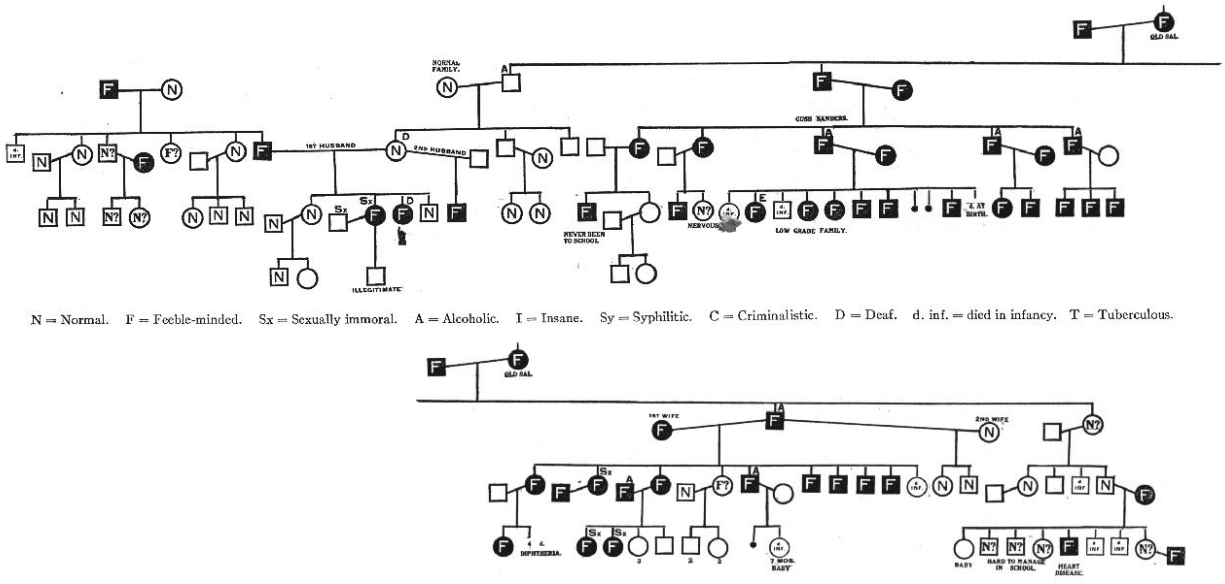


Figure 43.3: Kallikak family pedigree (Source: http://bit.ly/kallikak)

Goddard's conclusion, that the reproduction of people with such hereditary feeblemindedness should be limited, was soon institutionalized in compulsory sterilization legislation in the USA and then in other countries (see Wikipedia (N.d.*f*) on rise and decline of eugenics).

[Diagnosis by genetic type/sequence, Origin by descent]

44. Prenatal diagnosis

Selective abortion following prenatal diagnosis allows parents to decide not to have a child with certain conditions, including chromosomal abnormalities. (This is different from prenatal diagnosis for some cases of physical abnormalities, such as spina bifida (Wikipedia. N.d.*q*), in which corrective surgery may be attempted before the child is born.)

Complications

1. The most obvious complication is that in most cases, prenatal diagnosis is moot if abortion is not possible (legally or otherwise) or acceptable to the parents. Other complications include the experience of parents when faced with initial positive diagnoses that are not confirmed after subsequent testing, the risk of miscarriage following the common forms of testing, and other ethical issues reviewed well in Wikipedia's entry on prenatal testing, specifically the subheading "Ethical Issues of Prenatal Testing" (Wikipedia N.d.*o*)."Prenatal Testing").

2. Genetic counselors and clinicians tend to treat a positive diagnosis as more serious than parents (reference needed). The guidelines for neutrality in genetic counseling do not speak to the issue of a couple's preparation to make a decision if they get a positive diagnosis. For example, by far the most common prenatal diagnosis is Trisomy 21, Down syndrome. A couple who takes time to visit DS support groups and meet DS families may have a chance to explore whether their family and relationship could accommodate a DS child than one that has not. The last few decades have seen enormous changes in social acceptance and support for DS children and adults and many improvements in medical treatment and timely physical therapy (National Down Syndrome Society, N.d.). How much about actually existing people with DS is known by the 50-85% of parents who abort their fetus in the USA after receiving a diagnosis of DS (Natoli et al. 2012). (Rapp (1988) provides an early account of multiple voices that might be heard in prenatal screening for DS.)

3. Some might argue that prenatal diagnosis and selective abortion would reduce society's burden in having to give special care for very disabled people and thus free funds for general health care, education, etc. for the mildly disabled. Does this freeing of funds happen? The counter-proposition would be that such "genetic purification" in practice works against tolerance for the usual range of variation and measures to care for the abnormal. Is that happening? (To understand the logic of the counter-proposition consider an analogy: The health and fitness boom since the 1980s seems to have reduced tolerance for plump, "overweight" people. Those who have kept themselves trim tend to think that overweight people ought also to be able to do something about their figures.)

[Diagnosis by genetic type/sequence, Therapeutics & other interventions]

45. Address rare genetic diseases

According to Rodwell and Amyé (2014), rare diseases, defined as affecting 0.5 per 1000 people, are primarily "genetic diseases, the others [including] rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases..." (p. 6). If genetic diseases are defined as those that can be associated with point mutations in a gene, deletion of a gene, extra or deleted chromosomes, and repeated sequences (Wikipedia N.d.*j*) then most genetic diseases fit into the rare genetic disease category (Genetic Alliance UK 2014). At the same time, because rare diseases add up to affecting 6-8% of Europeans in the course of their lives (Rodwell and Amyé 2014, p. 6), it would be valuable to address them better, which means addressing the problems that:

> research on rare diseases is not only scarce, but also scattered in different laboratories throughout the EU. The lack of specific health policies for rare diseases and the scarcity of expertise, translate into delayed diagnosis and difficult access to care. This results in additional physical, psychological and intellectual impairments, inadequate or even harmful treatments and loss of confidence in the health care system, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. Misdiagnosis and non-diagnosis are the main hurdles to improving quality of life for thousands of rare disease patients (Rodwell and Amyé 2014, p. 6).

Complications

1. In one sense the problems just listed are complications; in another sense they form the readily acknowledged starting point for anyone interested in rare genetic diseases.

2. The genetic diseases listed in Genetic Alliance UK (2014) as more common than 0.5 per 1000, include ones, such as otosclerosis, that are deemed hereditary but with "penetrance and the degree of expression. so highly variable that it may be difficult to detect an inheritance pattern" (Wikipedia N.d.*m*).

3. Moreover, the same listing omits the most common genetic condition, namely, Down syndrome or Trisomy-21, which occurs in around 1 in 700 live births (Centers for Disease Control 2018).

4. As is widely recognized, the frequency of rare genetic diseases varies widely among populations according to geographic origin (Nussbaum et al. 2007), as may be explained if the mutation arose by chance in a small population and was carried down in descendants.

5. The tests to detect genetic diseases are of variable quality, leading to efforts at improvement, such as a project to "develop a model system for assembling, analyzing, disseminating and updating existing data on the safety and effectiveness of DNA-based genetic tests and testing algorithms" (Centers for Disease Control N.d.a, N.p.) (for more detail, see also Centers for Disease Control N.d.b).

6. The efforts of well-organized parental advocacy groups may, often by forming alliances with specific

medical research teams, secure funding to address the prenatal diagnosis or post-natal treatment of rare debilitating genetic disorders (Panofsky 2011).

7. Once the genetic basis of a condition is identified, there are implications for how the existing group of people with that condition are viewed, as evident in the “Endangered species” t-shirt campaign of the Little People of America (Taussig et al. 2003).

[Diagnosis by genetic type/sequence, Therapeutics & other interventions]

46. Understand sex difference.

Most people who identify as men have an X and a Y chromosome, while most people who identify as women have two X chromosomes. Understanding what genes are on the X versus the Y chromosome and when/how those genes are activated over the life course (beginning prenatally) is a way to examine the basis of sex differences. Similarly, for the different systems of sex determination across the animal kingdom (Wikipedia N.d.*p*).

Complications

1. Some sex determination systems in animals depend on environmental cues, such as the temperature during incubation of eggs in crocodiles.

Restricting the discussion to humans:

2. Not all humans match the pattern XY=identify as male; XX=identify as female.

3. Even for people who do match the preceding pattern, for most traits, the range for females and males overlaps. Of course, as noted in Chapter 39 the fact that variation within a group is of larger than variation between the average of the groups does not mean that the groups cannot be distinguished or that it is impossible to tell if a person is male or female.

> Let me affirm this last point with an example from a course I once took in multivariate statistics. We could not say with confidence whether a student was male and female on the basis of their height—there was too much overlap of the ranges—or, for the same reason, on the basis of their hip circumference. Yet a simple linear function that subtracted hip from height was very reliable in discriminating male from female students. [In Figure 46.1] height would be the x-axis, hip the y-axis; the squares the males, the triangles the females (Taylor 2011a).

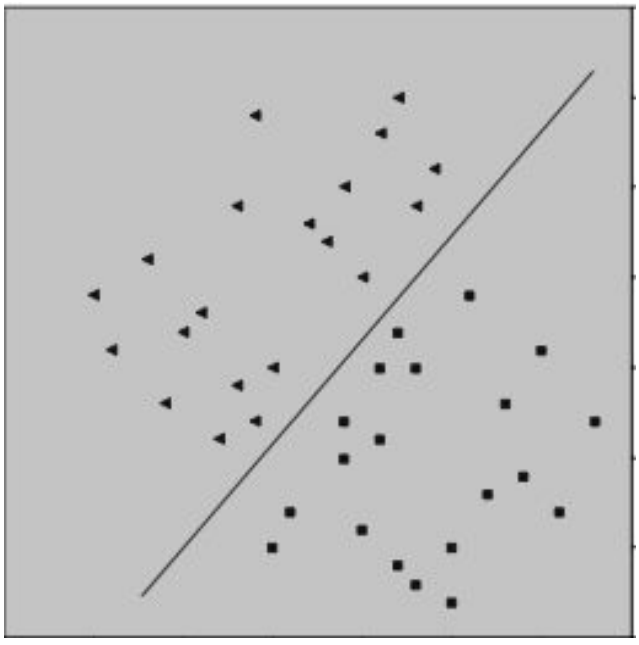


Figure 46.1: Discriminating male from female students. Adapted from Sesardic (2010) in Taylor (2011a)

This said, the combination of variables can differ from culture to culture and over historical time. In any case, the separability of groups on the basis of a combination of variables does not provide grounds for using an individual´s membership in a group to formulate reliable expectations or make pre-judgements about traits for any given individual.

4. Moreover, most discussions of differences between males and females are about gender, not genital and gonadal sex. In a culture that emphasizes gender differences and justifies large inequalities in the average power that identified-as-males and identified-as-females assume, people can accentuate or be forced to conform in various traits, such as aggression, to the average for their group. In other words, the culturally shaped ratio for a given trait of variation between the average of the genders to variation within a gender to may be larger than it would be if gender were simply given by chromosomal sex, or even by genital and gonadal sex.

5. Given the complex intersection of processes involved in sex and in gender development, and the complex intersection of these two phenomena, it becomes difficult to establish a method to determine the effect of any given gene.

6. Fausto-Sterling (2000) provides a rich account of the complexities of sex, gender, sexuality for humans.

[Biomedicine, gender, genetics, sex]

47. Revolutionary potential

The once science-fictional idea of “genetic engineering,” with its implications of altering the characteristics of human beings to ward off disease or to create armies of obedient slaves, has taken a long step toward reality in the last two years (McElheny 1975, p. 37).

The world’s oceans have been charted and its continents mapped. Today, a new kind of cartography is in progress, the mapping of the human genes and chromosomes, the microscopic biological structures that are the chemical basis to human identity. The effort is one of the key expressions of a revolution in genetics, and is facilitated by recently perfected tools of biological research and impelled by the hope that the new knowledge new research yields will help in the detection of genetically based diseases (Schmeck 1975, p. 188).

A revolution in the understanding of the genetics of plants will develop within approximately the next five years, a scientist said at a symposium. on the subject of genetic engineering applications to agriculture (Schmeck 1982, p. 00007).

How far and fast the field [of genetics] has come was abundantly apparent at a recent major international meeting in Toronto. Many, perhaps most, of the scientific reports given there would have been incomprehensible to geneticists as recently as a decade ago. Some would have been derided as fantasy. But today the revolution of modern genetics that began 35 years ago when the structure of the genetic material DNA was discovered has entered a new time of acceleration. “Genetics is a great engine driving the advancement of knowledge in a whole host of fields in biology,” said Dr. Philip Leder of Harvard Medical School, a major figure in modern research on gene functions (Schmeck 1988, p. 00001).

Convinced that advances in molecular biology and molecular genetics are transforming the theory and practice of medicine, the American Medical Association is virtually shouting at the nation’s doctors to pay attention. It is publishing more than 150 articles on advances in molecular genetics in 11 medical journals today, devoting its resources to pointing out that the genetics revolution is well under way (Kolata 1993, p. 00017).

This spring, Joe Tusek and many of his fellow farmers here in western Illinois will plant soybean seeds fortified with a biological weapon borrowed from the petunia. The genetic alteration will enable the farmers to cut costs by dousing their crops with Roundup, a cheap but powerful Monsanto herbicide that would kill normal soybean plants along with the weeds. Mr. Tusek, like thousands of other farmers across the United States, is volunteering as a foot soldier in a revolution more than two decades in the making. Since the mid-1970’s when scientists discovered an easy way to make copies of the genes that control the shape and behavior of all living things—and then how to move them among species—visionaries began predicting a new day in agriculture. Genetic engineering, as they called it, promised healthier food, more predictable harvests, fewer synthetic pesticides and more efficient use of water (Feder 1996, p. 3003003).

“There will be enhancements to life span, alterations to personality, like intelligence,” says Dr. Gregory Stock, the director of the Program on Medicine, Technology and Society at the University of California at Los Angeles. “In the not-too-distant future, it will be looked at as kind of foolhardy to have a child by normal conception.” Genetic research has always posed vexing social and ethical issues. But there may be no more complicated question than how the fruits of the genetic revolution should be used and, most important, who should have access to them. In the last century, eugenics was about the exercise of power and ideology. In the next, it may be about money (Stolberg 2000, p. E0007).

> For more than a decade, the public has been primed to expect an imminent revolution in genomics that would be the key to overhauling a broken medical system. Indeed, the promise of personal genomics is tantalizing: It could improve individual health by providing personalized risk information about diseases such as cancer, diabetes, heart disease and obesity, and about how individuals metabolize drugs, whether they are carriers for certain diseases and even what personality traits they are likely to have. This promise suggests a different landscape for health care, one in which individuals would actively participate in understanding and shaping their personalized health profiles. Equipped with their personal genomes, patients could choose healthier lifestyles and thereby achieve better health outcomes (Vernez and Lee 2011, p. 266.).
>
> etc. etc.

Complications

Who is involved in deciding what research in genetics is undertaken? What room is there/has there been for citizens to influence the course of science? ...and the application of results?

Who gains? What should we expect to happen as a result of aspects of “life” becoming commodified? (Rowling (1987) suggests that, once a market for a thing originates its production and exchange become tied up in increasingly complex social relations, in particular concerning: trade and the different levels of intermediaries; and control of production processes and the labour involved.)

What alternative paths to improvement are given less emphasis or not pursued? (E.g., Identification and reduction of environmental factors involved in increases of many cancers?)

Where does this lead to? (In the account of Yoxen (1986), there is no absolute technological inevitability in the sequence: prenatal screening & selective abortion -> somatic cell therapy -> germ cell (&early embryo) modification -> enhancement of specific genetic traits -> enhancement of more complex attributes. However, each step would make the next more feasible. Yoxen proposes that the public should discuss the implications and so individuals can make choices that enhance their freedom, self-esteem and sense of responsible reproductive behavior.)

[Production]

48. Build on something people have been doing for thousands of years

> The field of genetic engineering remains a heated topic of discussion in today's society with the advent of gene therapy, stem cell research, cloning, and genetically modified food …. [However] this relationship of biotechnology serving social needs began centuries ago (Wikipedia N.d.*h*).
>
> Dr. Fletcher [N.I.H.] said he sees no reason to restrict experiments in plants or animals unless the research is not meritorious or it involves extraordinary suffering. The mere fact that an experiment involves the manipulation of genes is not "in and of itself extraordinarily important," he said. "The whole subject of genetics has been shrouded in religious mystery, as if genetic experiments were not the business of human beings..." (Boffy 1987, p. 00001).
>
> "Nothing gives me cause for alarm about the patenting of life," Mr. Capron [USC Law Professor] said. "The scare words 'patenting of life' and 'creating life in the laboratory' are just that, scare words. They make it sound like very radical things are going on when in fact very simple things are being done." (Strolberg 2000, p. E00007).
>
> From the dawn of civilization, mankind has been modifying plants at the genetic level to suit its needs, and the fates of human society and agricultural crops have been inextricably linked and mutually interdependent ever since. Agriculture allowed humans to abandon hunter-gatherer behavior, in turn spawning broader economic and cultural development (Prakash and Conko 2003, N.p.).
>
> When the first genetically engineered crops came on the market. in the mid-1990s, people like me–plant breeders and the seed industry–tended to say, "Oh, gee, it's just a logical extension of what plant breeders have been doing all along. There has been a profound process of genetic modification since the dawn of settled agriculture until now..." (M. Smith quoted in Hirsch 2014, N.p.).
>
> From a scientific perspective, ...currently approved GMOs are safe (Janabi 2014, N.p.).

Complications

1. M. Smith (Hirsch 2014, n.p) went on to say: "Genetic engineering is a new and different way to do that," which invites the questions: Different in what ways? One answer is that genes are inserted into a range of varieties for commercial release that is much smaller than was previously available (except when hybrid varieties had already reduced that range from original open-pollinated sources). The sources of seeds suitable for specific environments has been reduced.

2. Moreover, in an open-minded spirit, Hirsch (2014), quoting Smith goes on to note:

> The fear that GMO foods are not safe is valid, she said, adding other aspects raise concerns such as the financial power of seed companies like Monsanto, all the herbicides used on genetically engineered crops, and the impact on the larger ecosystem. But, she said a lot of those worries are based on value judgments, not science.

This invites the question: Who gets to decide or deliberate on what values go into the breeding, ownership, release, and application of plant varieties in the age of genetic engineering?

3. In what contexts do scientists appeal to the revolutionary potential of genetic engineering versus it building on something people have been doing for thousands of years? (see Chapter 47).

4. Both sides of pro- and anti-genetic modification in food production accuse each other of employing the arts or strategies of war: “[W]hy do the ideas of the anti-GMO movement need the strategies of war to be taken seriously?” (Janabi 2014, n.p.) versus “GMO Pushers and The Art of War” (Kucinich 2014).

[Variation within & between groups]

49. Biotech/Pharma funds it

The 1970s saw researchers in molecular genetics first argue that science progresses when free from outside direction--in the form of government restrictions on genetic engineering--and later argue that science progresses when scientists are free to receive funding (and often direction) from private corporations--including corporations started by academic researchers. In 1980 the Bayl-Dole act (Wikipedia N.d.*b*) in the USA allowed private corporations to profit from commercializing products of research that had been funded by the government.

Universities began investing in biotechnology (biotech), whether by licensing results of research conducted by their faculty, building centers aimed at attracting partnerships with biotech corporations, or allocating parts of their endowments to biotech stocks (which were increasingly stocks of pharmaceutical companies that acquired biotech startups). Growth in the biotech sector (a term that came to be seen as more than research based on genetics) followed (Wikipedia N.d.*h*), with trends illustrated by this plot [Figure 49.1] of market capitalization in the USA (where the vertical scale on the left is $billion and DJIA refers to Dow Jones Industrial Average on the right):

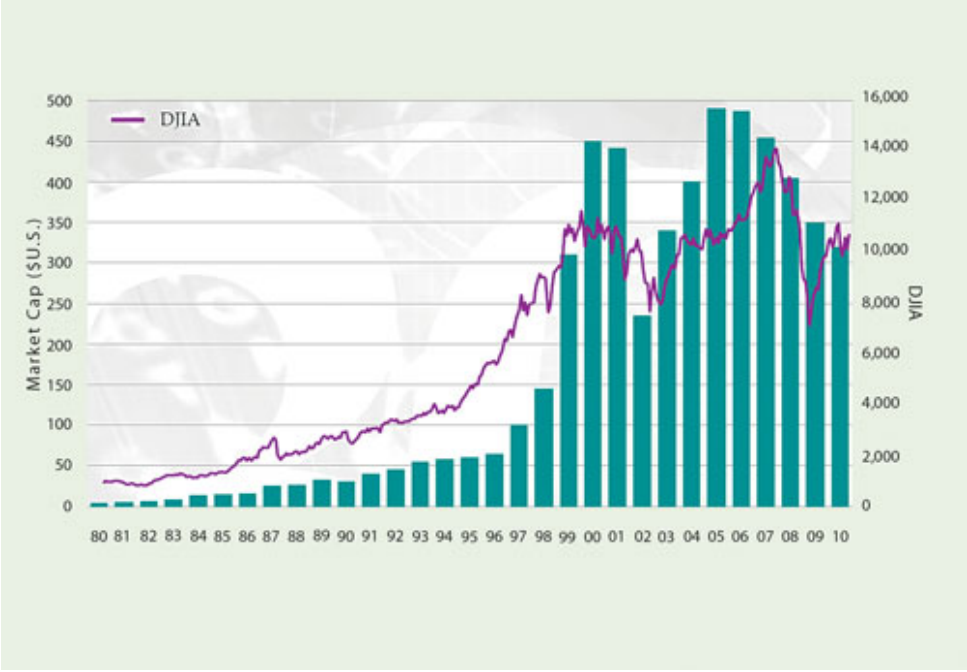


Figure 49.1: “Historical Biotech Market Cap” plot from Burrill (2011, N.p).

It is now difficult if not impossible to conceive of or get funding for biotechnology research without thinking in the terms of commercialization, as illustrated by leading journals such as Nature spinning off new journals, such as Nature Biotechnology, and the articles in the 2012 special edition on Commercializing Biomedical Research (“Focus on Commercializing Biomedical Research,” 2012). (For a more detailed history of corporate and government shaping of scientific innovation in biotech, see Malerba and

Orsenigo 2001.)

Complications

By the early 1990s, the speculative dimension was evident in investment in biotech: Should one buy stocks based on optimism about a firm's future profitability and aim to sell early if they begin to decline? (Feder 1991).

Moreover, a firm's prospects may rise with a new innovation and fall when a competitor overtakes the speed the firm had achieved (Herper 2014).

> Wall Street turned its back on biotech many times over the last 30 years. During those periods, capital was more expensive and difficult to obtain (Burrill 2011, N.p.)
>
> Universities have been pulled into the realm of technology maturation to fill a void in early stage investing (Borchardt 2012).
>
> The biotech investment community needs to look beyond the existing pools of funding and talent to galvanize biomedical innovation (N.a. 2012).

50. Genomics is “promising” in a “high-speed, high-tech, and high-finance world”

As described by Mike Fortun in his 2008 book, *Promising Genomics*, a biotech company was given rights to knowledge and its application derived by connecting health data with genomic data for all of Iceland’s citizens. As described in a review of the book, Fortun:

> comes neither to fortify nor to condemn contemporary conjunctures of industry, science, and statecraft. Rather, Fortun seeks to demonstrate the molten character of “responsibility” in genomics, when the making of genomes and their properties unfolds through such heterogeneous but conjoined practices as scrutinizing nucleotides, keeping an eye on the investment regulations of the Securities and Exchange Commission, and debating questions of privacy/privatization in national legislative bodies. Speculating on genomics— scientifically, financially, politically—requires an analytical and ethical openness rather than a too-sure-of-itself a priori bioethics. It requires, argues Fortun, a special attention to promises: how they are made, what they require, and why they almost always generate futures that, in their stipulation, have an uncanny way of folding back into and (re)orienting the present (Helmreich 2009, p. 477).

Complications

DeCODE filed for bankruptcy in 2009, (Wade 2009) but was bought out by Amgen in 2012 (Baker 2012). The firm continues its work, but now with less attention in investment circles and the media (DeCODE N.d).

Sometimes something else more promising, such as apps for mobile devices, emerges and the investment gets withdrawn from areas, such as biotech, where the promises had been seen to be [figure 50.1] (Crawford 2013).

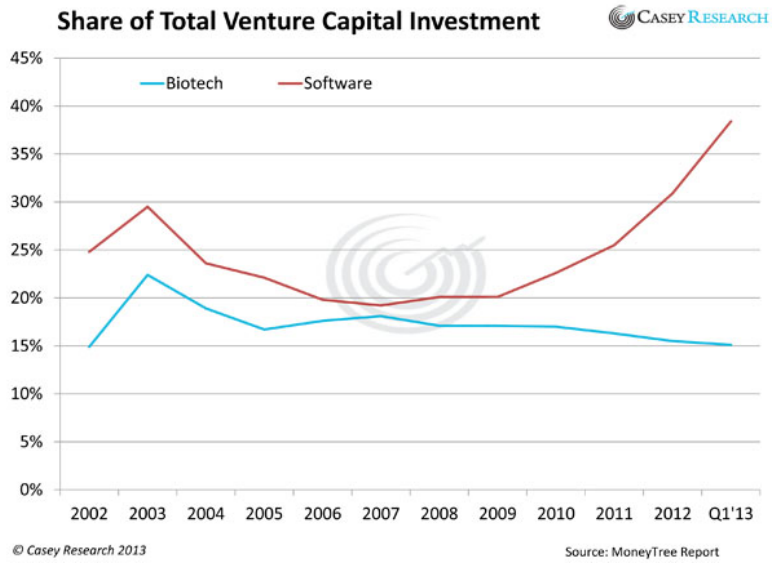


Figure 50.1: Image from the article “Is biotech funding drying up?” (Crawford 2013).

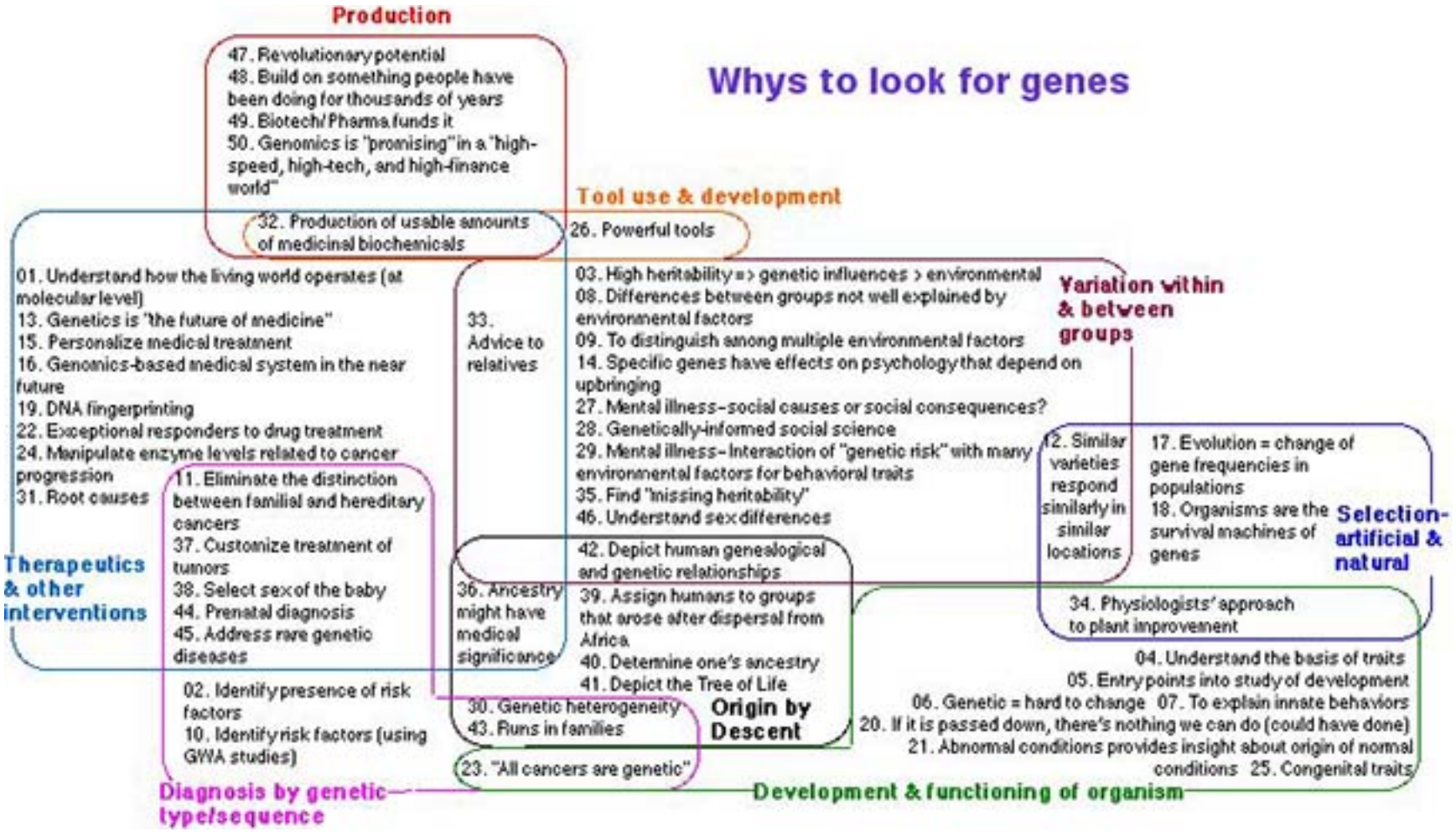
[Production]

Epilogue: Whys to look for genes, a map

The fifty posts appear to fit under one or more of the following eight categories:

- Development & functioning of organism
- Diagnosis by genetic type/sequence
- Origin by Descent
- Production
- Selection-artificial & natural
- Therapeutics & other interventions
- Tool use & development
- Variation within & between groups

The map below is arranged to show posts that fit in more than one category.


Whys to look for genes
Production
47. Revolutionary potential
48. Build on something people have been doing for thousands of years
49. Biotech/Pharma funds it
50. Genomics is "promising" in a "high-speed, high-tech, and high-finance world"
Tool use & development
32. Production of usable amounts of medicinal biochemicals
26. Powerful tools
01. Understand how the living world operates (at molecular level)
13. Genetics is "the future of medicine"
15. Personalize medical treatment
16. Genomics-based medical system in the near future
19. DNA fingerprinting
22. Exceptional responders to drug treatment
24. Manipulate enzyme levels related to cancer progression
31. Root causes
33. Advice to relatives
03. High heritability => genetic influences > environmental
08. Differences between groups not well explained by environmental factors
09. To distinguish among multiple environmental factors
14. Specific genes have effects on psychology that depend on upbringing
27. Mental illness–social causes or social consequences?
28. Genetically-informed social science
29. Mental illness–Interaction of "genetic risk" with many environmental factors for behavioral traits
35. Find "missing heritability"
46. Understand sex differences
Variation within & between groups
12. Similar varieties respond similarly in similar locations
17. Evolution = change of gene frequencies in populations
18. Organisms are the survival machines of genes
Selection-artificial & natural
Therapeutics & other interventions
11. Eliminate the distinction between familial and hereditary cancers
37. Customize treatment of tumors
38. Select sex of the baby
44. Prenatal diagnosis
45. Address rare genetic diseases
42. Depict human genealogical and genetic relationships
36. Ancestry might have medical significance
39. Assign humans to groups that arose after dispersal from Africa
40. Determine one's ancestry
41. Depict the Tree of Life
34. Physiologists' approach to plant improvement
02. Identify presence of risk factors
10. Identify risk factors (using GWA studies)
30. Genetic heterogeneity
43. Runs in families
Origin by Descent
04. Understand the basis of traits
05. Entry points into study of development
06. Genetic = hard to change 07. To explain innate behaviors
20. If it is passed down, there's nothing we can do (could have done)
21. Abnormal conditions provides insight about origin of normal conditions 25. Congenital traits
23. "All cancers are genetic"
Diagnosis by genetic type/sequence
Development & functioning of organism

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The working paper is dedicated in memory of Ann S. Blum (1950-2015)—most of the daily blog posts were drafted in the waiting room for her unfortunately unsuccessful chemotherapy sessions.

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