Chapter 7

Mendelian Traits

This chapter describes several “Mendelian” traits that have relevance to human behavior. A Mendelian trait or disorder is one that is due to a single gene and not to the effects of a large number of genes. The purpose is to reinforce learning and to illustrate several new concepts about how a gene can relate to behavior. (Zucker et al., 1996a)

7.1 Terminology

Let us now examine three central terms that describe the relationship between a single gene and a phenotype. The first of these is penetrance of a genotype. Penetrance is defined as the probability that a person exhibits a phenotype given that the person has the genotype for that phenotype. When applied to disease—as the term usually is—penetrance refers to the probability that a person will develop the disorder given that the person has the genotype for the disorder.

Penetrance is a conditional probability, so it is literally a number that can logically range from 0 to 1.0. Complete penetrance refers to disorders and traits where the probability is very close to 1.0. Thus, if a person has the genotype, s/he will almost always develop the disorder. Huntington’s disease and cystic fibrosis are two examples of disorders with complete penetrance. Incomplete penetrance occurs when the probability is significantly less than 1.0. Marfan’s syndrome is a classic example of a disorder with incomplete penetrance. About half of the people with the gene for Marfan’s syndrome actually develop the full syndrome.

The second phenomenon relating genotype to phenotype is pleiotropism or pleiotropy. Pleiotropy refers to the phenomenon that a single gene can influence more than a single phenotype. For example, the Huntington’s disease gene can influence several different phenotypes. Two phenotypes—incllect and movement—will be used here to demonstrate pleiotropism. Huntington’s disease (HD) usually has an onset in midlife around age 40 and is initially noticed by increasing clumsiness. As the disorder progresses, the person gradually develops
involuntary motor movements in the head and limbs. The loss of voluntary motor control worsens and the person eventually loses the ability to walk and feed himself. Even before these motoric problems are noticeable enough to diagnose HD, there is often a decline in intellectual functioning that is imperceptible to the person or his family. As HD progresses, the decline accelerates and becomes noticeable. Eventually dementia (the progressive and irreversible loss of cognitive functioning) occurs. Hence, one aspect of pleiotropy for the HD gene is its influence on both cognitive processes as well as motoric behavior.

The third phenomenon relating genotype to phenotype is variable expressivity. Variable expressivity applies to a continuous or quantitative trait, i.e., a trait that everyone possesses but has different amounts of it. Height is an example. Variable expressivity occurs when a single gene results in a range of phenotypic values for a single trait. A classic example is the relationship between intelligence and phenylketonuria (PKU). When untreated, PKU reduces the average cognitive ability of affected individuals. However, PKU exhibits variable expressivity because it results in a significant range of IQ scores. Some children with untreated PKU are severely mentally retarded while other untreated children are in the low, normal range of IQ. As you read about Mendelian traits and disorders in the following pages, keep in mind these three basic phenomenon—penetrance, pleiotropy, and variable expressivity.

7.2 Phenylketonuria

Phenylketonuria or PKU is the poster child for behavioral genetics because an effective environmental intervention can ameliorate the damaging effects of the disorder. Clinically, untreated PKU babies are physically normal at birth but develop symptoms within the first year of life. These symptoms include mousy smelling urine and sweat; small head size (microcephaly); motoric abnormalities in posture, stance, and gait; light colored skin, blond hair, and blue eyes (hypopigmentation); eczema; seizures; intellectual deficiency; irritability; and hyperactivity. There are several lessons that PKU teaches us about genes. They are a metabolic block, therapeutics for a genetic disorder, pleiotropism, and allelic heterogeneity. We discuss each in turn.

7.2.1 Metabolic block

PKU is a recessive disorder—the disorder is expressed only when two deleterious alleles come together in the same individual. People who inherit one normal allele and one deleterious allele are phenotypically normal but are often referred to as carriers. A recessive mode of inheritance is common for disorders involving metabolic enzymes. As a general rule, the mRNA transcripts and the translated enzymes from only one DNA segment (i.e., allele) is sufficient to maintain metabolism.

The genetic defect underlying PKU is an abnormality in the enzyme phenylalanine hydroxylase (PAH), the gene for which is located on the long (i.e., q)
Figure 7.1: Metabolic pathways for phenylketonuria and other metabolic blocks.
arm of chromosome 12. Part of the metabolic pathway that involves this enzyme
is depicted in 7.1. Let us spend some time going through this figure so that we
can learn about the pathways from gene to behavior. The relevant portion of
the figure is the upper, left quadrant.

Phenylalanine is an amino acid and, hence, a necessary constituent of pep-
tides, proteins, and enzymes. The two major sources of phenylalanine are diet
and the breakdown of cellular proteins and enzymes into their basic amino acids;
hence arrows are drawn from diet and tissue proteins into phenylalanine in the
figure. Three things occur to the phenylalanine in our system: (1) it is used to
build peptide chains, depicted in the figure by the arrow from phenylalanine to
tissue proteins; (2) it acts as a substrate for the construction of another amino
acid, tyrosine; and (3) it is degraded into phenylpyruvic acid and other phenyl
derivatives. The enzyme PAH is responsible for the second of these—the con-
version of phenylalanine into tyrosine. When PAH is defective, then it acts as a
metabolic block. The term metabolic block is very important in genetics because
it describes the mechanism for a large number of Mendelian disorders. Gener-
ally, it refers to a defective enzyme that results in the build up of precursor
substances in a metabolic pathway. In PKU, phenylalanine and phenylpyruvic
acid build up in the body and the amount of tyrosine is reduced. By some
unknown mechanism, damage occurs to the nervous system, leading to mental
retardation and some of the neurological symptoms noted above.

Figure 7.1 also illustrates a series of other metabolic blocks that occur in
the pathways of tyrosine metabolism. For example, a block in the conversion
of tyrosine to thyroxine results in a syndrome called goitrous cretinism and a
block in the conversion of DOPA to melanin results in a form of albinism. It
is not necessary to know these syndromes. The important point is that there
are many metabolic blocks that lead to phenotypic irregularities and medical
disorders.

7.2.2 Therapeutics: Diet

At this stage, let us postpone discussion of the metabolic pathway to focus
on the second major lesson from PKU—an effective environmental therapy.
Because something associated with excess phenylalanine is responsible for PKU
and because diet is a major source of phenylalanine, restricting the dietary intake
of phenylalanine sounds as if it might prevent the harmful symptoms of PKU.
Indeed, this is the case. Currently all newborns in modern industrialized nations
are pricked on a heel and the small quantity of blood is tested for excessive levels
of phenylalanine and phenylpyruvic acid. If this test is positive, a more sensitive
test is performed to confirm the diagnosis. The parents are informed, and the
infant is placed on a special formula. The infant cannot have mother’s milk, cow
milk, or standard formula, and after weaning, must avoid all foods with high
levels of protein and be maintained on special dietary supplements. In typical
medical practice, the diet is individualized. Blood levels of phenylalanine are
constantly monitored and the diet adjusted to keep the levels within safe limits.
Many PKU children will eventually be able to tolerate certain fruits, vegetables,
and grains that are low in phenylalanine. The biggest limiting factor is the child’s adherence to the dietary recommendations.

If the diet is adhered to, then the mean IQ of children with PKU does not differ markedly from normals. They do, however, show a number of minor deficits in cognition and psychological functioning. Many finer issues about the diet are still debated—e.g., the levels of blood phenylalanine that are considered safe (Diamond, 1994; Trefz et al., 2011); the age at which the diet may be discontinued, if indeed it can be discontinued at all Azen et al. (1996); Burgard et al. (1996); Griffths et al. (1995); Trefz et al. (2011); and the importance of supplementing the diet with tyrosine (Diamond, 1996). There is an active research agenda into predicting when and for whom the diet may be safely discontinued. Despite such uncertainties, PKU is a clear indication that a genetic influence on a disorder is no cause for therapeutic nihilism. Even if something is 100% genetic, the environment may still present an effective way of dealing with it.

7.2.3 Pleiotropism

We can now return to the metabolic pathway. Because the enzyme PAH is damaged, the amount of tyrosine is reduced in PKU. Tyrosine itself is converted to DOPA which, in skin cells, eventually produces pigment (melanin). The reduction in tyrosine and hence, pigment, is apparently the reason why the skin, hair, and eye color of individuals with PKU is lighter than that of their normal sibs.

Tyrosine also acts as a precursor to DOPA which is eventually synthesized into the neurotransmitters dopamine and norepinephrine. It is possible—although not really known—that the some behavioral consequences of PKU may be associated with deficits in these neurotransmitters, especially dopamine (Diamond, 1996).

We have now encountered the second major lesson that PKU has for the genetics of behavior—pleiotropism or the phenomenon of a single gene affecting more than one phenotype. The PAH locus, for example, effects anatomy (small head size and undermylenization of the nerve cells) and physiology (reduced melanin production) as well as several domains of behavior—cognition, personality, and motor functioning. Pleiotropism is far from rare among genetic disorders. Indeed, the eminent geneticist Sewall Wright stated that all genes are pleiotropic.

A moment’s reflection on the metabolic pathway in 7.1 gives a convincing illustration of Wright’s concept of universal pleiotropism. The biochemical systems mediated by enzymes and receptors (and thus by the genes that code for these enzymes and receptors) are highly interconnected with feedback loops and other regulatory mechanisms to insure that the system does not capriciously shut down or turn into a runaway process that damages the organism. If a monkey wrench is thrown into such an interdependent system—just like the defective PAH enzyme is thrown into the metabolic pathway in Figure 7.1—then there will be a large number of consequences both upstream and downstream from the point that the monkey wrench does its damage. With this in mind, it would
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actually be very surprising to find that a major defect in a single gene would influence one and only one phenotype.

Our previous consideration of evolutionary principles is also consistent with universal pleiotropism. Evolution is a pragmatic tinkerer with no forethought beyond fixing something so that organisms can reproduce at an acceptable rate. Hence, it is likely to alter something that already exists in an organism’s biochemistry rather than design a system de novo to solve a reproductive problem. If an organism with pigment needs a specialized neurotransmitter, then evolution is more likely to tinker with the enzymes that act on tyrosine to let it eventually produce dopamine than start out with a brand new substrate and construct a novel metabolic path for it. Hence, it is not unreasonable for the evolutionist to find that the production of skin pigment has something to do with neurotransmission even though there is no logical connection between the two.

7.2.4 Allelic heterogeneity

Like most Mendelian disorder, PKU exhibits the phenomenon of allelic heterogeneity—the fact that many different alleles at a single locus can produce the same syndrome. Again, this is a logical consequence of what we have learned about the biological nature of the gene. There are many ways in which the DNA blueprint for the PAH enzyme can go awry and if any one of them happens, then the translated product of that DNA will not work correctly. As a result, over 500 different alleles at the PAH locus can cause the disorder (Scriver et al., 2003). If any two of these hundred or so alleles come together, then some form of PKU will result. Because there are so many different alleles, few people with PKU have the same nucleotide sequence at both of their PAH genes.

Allelic heterogeneity may be responsible for some of the variable expressivity in the disorder. Some alleles will result in no functional PAH. If someone inherits two of these, then the clinical manifestation will likely be severe. Other alleles may produce PAH enzyme but its functionality is impaired. Someone inheriting two alleles within this category may have milder manifestations. Again, there is an active research examining the correlation between the genotype and the phenotypic consequences from this allelic variation (Cleary et al., 2013; Koch et al., 2003b; Trefz et al., 1993b). Paradoxically, however, treatment success has, mercifully, impeded this research. As Mitchell et al. (2011) point out, “It is becoming more difficult to assess clinical phenotypes given that most individuals with PAH deficiency in developed countries are treated successfully.”

While allelic heterogeneity may explain some of variability in the clinical manifestations of PKU, it cannot explain all of it. DiSilvestre et al. (1991), for example, presented the intriguing case of three siblings all of whom had the same genes for PKU yet differed significantly in their clinical pictures.

A final lesson from PKU comes from examining the IQ distribution in untreated cases. Here, we must go back several generations to examine the relevant data because virtually all PKU cases in modern industrialized countries are now detected and treated at birth. Hence, untreated cases are rare.
When definitive tests for PKU were first developed, it was noted that some siblings of a PKU individual tested positive for PKU but did not suffer from severe mental retardation. Although few had IQ above the average in the general population, a significant number fell into the low normal range. Why? The reason for this is a mystery and is likely to remain a mystery for some time—it would be unethical and cruel to withhold the dietary intervention in order to identify those whose eventual IQs fall into the normal range. Still, this fact underscores the variable expressivity that can occur with PKU and IQ.

7.3 Fragile X syndrome

The fragile X syndrome (FXS) was first described by Martin and Bell (1943) although it took several decades to fully characterize the disorder. Initially called the Martin-Bell syndrome, its current name comes from karyotypes in which it appeared that a section of the X chromosome was close to breaking off from the main body. It is the the most common Mendelian disorder among folks with intellectual deficiency (ID, formally known as mental retardation). It is also the most common single gene disorder associated with autism and autism spectrum psychopathology (Budimirovic and Kaufmann, 2011; Wang et al., 2012). Despite this, FXS is not common in an absolute sense. Its prevalence is approximately 1 in 4,000 births in males and and 1 in 8,000 births in females, although like most Mendelian traits, there are wide differences in prevalence as a function of ethnicity (Peprah, 2012).

Several physical features are associated with FXS. These include flat feet, an elongated face with prominent forehead, jaw and ears, and in males, enlarged testicles (AKA macroorchidism) after puberty. These phenotypes are subtle mean differences from the average trait in normals, so it is not possible to diagnose the syndrome from them.

The most common medical correlates are neurological. They include seizures which often develop during childhood, problems in vision, and poor motor coordination. Later in life, those with FXS are at risk for developing a progressive neurological disorder characterized by tremor, ataxia (incoordination of voluntary movements) and dementia.

Rarely diagnosed at birth, most cases come to medical attention because of behavioral problems and irregularities during early development. These include delayed speech and language, hyperactive and impulsive behavior and problems in social interactions, especially poor eye contact. Not all children with FXS, however, demonstrate such symptoms. It is not unusual to discover a FXS child who is adapting well at home and at school but is diagnosed only because a younger sibling exhibits a more virulent form of the disorder. Hence, there is marked variable expressivity for behavioral phenotypes in this disorder.

This variable expressivity makes it difficult to arrive at precise prevalence estimates and figures about the syndrome’s association with ID and psychopathology. Only those cases with problems (and their affected relatives) come to the attention of doctors and researchers. We do not know the number of FXS in the
The gene responsible for FXS is located on the X chromosome (Xq27.3) and is called FMR1 (for fragile mental retardation 1). It codes for a protein called FMRP (fragile mental retardation protein) that is found in many tissues but especially in neurons. Not all of the many functions of FMRP are known, but it binds to RNA and together with other factors, inhibits translation. It is also associated with the transport of mRNA through the cytoplasm to the dendrites and synaptic buttons of the neuron Santoro et al. 2012. When the amount of FMRP is low, translation of some proteins is not inhibited, particularly in the dendrites. This may lead to the formation of an excess number of dendrites which is known to be associated with neurological problems.

The clinical severity of FXS is directly correlated with the amount of FMRP—the lower the amount of FMRP, the greater the severity Hagerman and Hagerman 2002. The most severely affected individuals are those with no detectable FMRP.

The reason behind the pathology is an abnormal number of trinucleotide repeats (nucleotides CGG) in an untranslated region of the gene close to a promoter (see Figure 7.2). All humans have a series of CGG repeats in this area, but in normals the number of repeats ranges from 6 to 44. Alleles in this range are called common. Alleles with repeats between 45 and 54 fall into a gray zone and are termed intermediate (Seltzer et al., 2012). Once the number of repeats exceeds 54, the allele is called a premutation because it is hypermutable (susceptible to mutations that further expand it). People with a permutation are called carriers. When a mutation expands it to 200 repeats or greater, the region

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1The cutoffs among common, intermediate and premutation alleles are a matter of debate.
becomes abnormally methylated and transcription is inhibited, sometimes to the point of completely silencing the gene. This is termed a “full mutation.”

The numbers separating common, intermediate, premutation and full mutation alleles should be regarded as “fuzzy” thresholds. Those with a premutation, for example, may still show some signs of FXS, particularly ataxia, later in life (Peprah, 2012; Turk, 2011). Similarly, the number of repeats within a premutation allele is correlated with the probability that it will mutate past the the threshold into a full mutation (Mandel and Biancalana, 2004). For this reason, not all researchers use the same cut offs for the various categories.

In males, there is almost 100% penetrance in the sense that all show some symptoms, however, mild. Because of variable expressivity, however, the mildness of the symptoms may result in minimal impairment. Because of the rarity of an X chromosome with a full mutation, almost all affected females are heterozygotes. In females, however, the syndrome exhibits partial or incomplete penetrance with a wide range of severity in symptoms. On average, however, the symptoms in females are less severe than those in males.

7.3.1 Trinucleotide repeats

Unstable and expanding trinucleotide repeats are a mechanism for several neurological disorders, not merely for Fragile X. They cause Huntington’s disease, some forms of muscular dystrophy and some dementing illnesses involving the frontal and temporal areas of the brain (Nelson et al., 2013). In FXS, the mechanism is abnormal methylation which reduces transcription of a gene whose product is necessary to limit translation of certain proteins. In almost all of the other disorders, the mechanism is different.

While the trinucleotide in FXS is CGG, it is CAG in the other disorders and the repeat occurs in a coding exon of the gene. The CAG codon codes for glutamine, so the result is a long string of glutamine amino acids somewhere in the protein. From there, these polyglutamine disorders remain mysterious with many more questions than answers. Why are individuals asymptomatic at birth and early childhood but become affected mostly during the middle adult years? Why does pathology involve three nucleotides and not two or four?

The discovery of the trinucleotide repeat association with pathology has prompted considerable research into trinucleotide repeats and psychiatric disorders. To date, no firm associates have been reported.

7.3.2 Anticipation

Anticipation is the phenomenon in which the age of onset decreases and/or severity of a disorder increases in more recent generations of a pedigree. This was a controversial topic in genetics, but work on Fragile X and other trinucleotide repeat disorders confirmed it as a phenomenon. The story begins with Stephanie Sherman’s analysis of pedigrees with Fragile X (Sherman et al.,

See Seltzer et al. (2012).
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1985b, 1984b). She and her colleagues noticed several instances in which the disorder was transmitted by an unaffected male. In ordinary genetics, both the mothers and the daughters of these male carrier should have the gene with equal frequency. Hence, the severity of FXS in the male carrier’s siblings should be the same as that in the male carrier’s grandchildren. But they were not. The severity in the male carrier’s grandchildren was greater than that in his siblings.

The reason for this paradox is the hypermutability of trinucleotide expansions. As one moves down the pedigree from ancestral generations to the current one, the length of the expansion increases. Hence, affected individuals in recent generations have longer expansions than those in distant generations. The result is often a decrease in age of onset for disorders like Huntington’s disease and an increase in severity for FXS as one moves down the pedigree.

### 7.3.3 Variable expressivity

Perhaps the most striking feature of Fragile X syndrome is its variable expressivity. Individuals with the full mutation (i.e., more than 200 CGG repeats) can have social behavior than ranges anywhere between social hyperexuberance and abnormal overdetachment. Although mean IQ is somewhere between 60 and 70, the standard deviation of IQ scores is not remarkably different from that in the normal population. Hence, some Fragile X individuals are within the low-normal limits and can profit from standard public education while others require special interventions for their cognitive impairment and learning problems. Some cases may exhibit socially engaging behavior; others may be characterized by inappropriate aggression.

7.3 presents a hypothetical pedigree that illustrates both anticipation and the variable expressivity of the Fragile X phenotype. The progenitor is the X chromosome carried by the male parent at the top of the pedigree. This chromosome has 29 CGG repeats, so he is normal. It is passed along intact to the first daughter. But in the genesis of the sperm that results in the second daughter, a mutation occurs that expands the CGG sequence from 29 to 125 repeats. The number of repeats in this daughter is now within the 50 to 200 range which means that the FMR-1 locus on this chromosome is now “hypermutable,” or at a very high risk of mutating to longer CGG repeats in future generations.

Because the X chromosome for this woman has 125 CGG repeats (and also because her other chromosome has a normal number of repeats), she is unaffected. However, when she generates her eggs, they have an increased probability of mutating to a longer series of repeats. (Actually, hypermutability is much more common in sperm than in eggs, so this woman is the exception rather than the rule.) A mutation occurs in one of her eggs and a sequence of 246 CGG repeats is passed to her firstborn, a daughter. This passes the critical level of 200 repeats, so this daughter may show mild signs of the syndrome but would probably be well within the normal range of behavior because she is “buffered” or protected by the good FMR-1 locus on her other X chromosome. For example, she may have an IQ that is lower than that predicted by her family history and she may show minor difficulties with attention, but these symptoms may
Figure 7.3: A pedigree illustrating anticipation.
not be noticeable enough to have her referred to a school psychologist.

The mutation also occurs in the X chromosome transmitted to her brother, who receives 288 CGG repeats. The difference between these 288 CGG repeats and the 246 repeats in his sister is relatively minor, but because the male lacks an extra X chromosome, he is not protected from its deleterious effects. He is likely to show features of the Fragile X phenotype, although they will be on the less severe side. For example, he may have learning difficulties at school, be diagnosed with mild intellectual deficiency, and exhibit enough attention problems and hyperactivity to qualify for a possible or probable diagnosis of ADHD.

His sister marries and has two children, both boys. The hypermutability of the locus is evident in the number of CGG repeats inherited by both of her sons. The first inherits a FMR-1 locus with 749 repeats. He is likely to show a full-blown syndrome with some irregularity in facial features, moderate mental retardation, marked attention difficulties, and other behavioral problems. He may be placed in a special education program for the developmentally disabled and also be given medication for ADHD. By bad luck, his brother also inherits the hypermutable X chromosome but the repeats in his case number 1036. He shows severe Fragile X. In addition to mental retardation, he could have the physical irregularities of facial appearance that make him appear “unusual” in a very amorphous and inarticulable sense to casual observers. He could have serious learning disabilities and problems with attention and concentration. In addition, his social behavior may be awkward enough that some psychologists might consider him as having autistic features.

7.4 Congenital adrenal hyperplasia (CAH)

Congenital adrenal hyperplasia (CAH) is a medical syndrome that illustrates genetic heterogeneity. In genetic heterogeneity, the same syndrome (or very similar syndromes) can appear from defects (or differences) at more than a single locus. A defect in any one of the loci can produce the syndrome. Albinism is another example of a genetically heterogeneous syndrome.

In CAH, there is a metabolic block somewhere in the synthesis of cortisol from cholesterol in the adrenal gland. 7.4 illustrates the metabolic pathway. There are five different steps in cortisol synthesis, and if any one of these steps is blocked then some form of CAH can result. There is a reduction of cortisol and a build of the precursors to cortisol synthesis. Like most metabolic blocks, the genes for CAH are recessive. That is, to exhibit the syndrome, one must have two defective alleles at a single locus.

The five forms of CAH have different prevalences. Over 90% of cases arise from the deficiency in the enzyme 21-hydroxylase. Note also the variability in medical outcomes. Four of the forms can be managed medically but 3β-OH-dehydrogenase deficiency remains lethal.

Having established that CAH is genetically heterogeneous, let us focus on the most common form of CAH, 21-hydroxylase deficiency. Because this is
an autosomal recessive disorder, it will occur in XY and XX individuals with equal frequency. XY individuals have normal external genitalia but often have problems such as high blood pressure (hypertension) and salt loss that require medical intervention.

The situation is quite different in the fetus who is chromosomally XX. Re-examine Figure 7.4. With the metabolic block, there is a build up of the precursor 17-hydroxy pregnenalone which also acts as a precursor to the synthesis of various androgens (masculinizing hormones). In the XX fetus, initial sex development proceeds normally, so the tissues develop into the usual internal sex organs—ovaries, fallopian tubes, etc. The high dose of male hormones, however, occurs at the time in embryogenesis when the external genitalia develop. This will change the development of these tissues away from the clitoris and labia and toward a penis and scrotum. The extent of virilization (i.e., masculinization) of external genitalia is variable. Differences can range from clitoral enlargement through ambiguous genitalia to genitalia that so closely resemble a male that they go unrecognized at birth. The typical medical intervention for the virilized girls is to surgically correct the genitalia to agree with chromosomal sex. They are then raised as girls. The intriguing feature of virilization for the study of behavior is the effect of the early dose of androgens on brain development. Prenatal androgens have been shown to influence early rough and tumble play, aggression, and copulatory behavior in both rodents and primates. Could the same be true of humans?

Sheri Berenbaum and her colleagues have begun systematic research into children with CAH. In one study, Berenbaum and Hines (1992b) her group tested CAH boys and girls and their unaffected siblings in a toy preference situation. The experimental paradigm, used extensively in past research on child...
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development, involves placing a child into a room with toys that are stereotypically “boyish” (e.g., a fire engine), stereotypically “girlish” (e.g., dolls) or neutral (e.g., a book). The child can freely play with any toy(s) that s/he chooses while an assistant records the toys that are played with and the amount of time played with each toy.

There is considerable individual variability in children in which toys they play with, but on average boys spend more time with the trucks while girls spend more time on the dolls. The control boys and girls in this study showed exactly this play pattern. The CAH boys were no different than the control boys. Indeed, there are no differences between CAH boys and control boys on a wide of sex-stereotypical behavior. This suggests that the extra prenatal androgen does not “super masculinize” a boy.

The CAH girls, on the other hand, exhibited a preference that resembled the control boys more than the control girls. Berenbaum and Hines were unable to find that parental treatment or degree of childhood illness could account for this and suggest that the masculinization of phenotypic toy preferences in these girls may have been due to the prenatal effects of androgens.

Other research suggests that CAH girls differ from their unaffected sisters (or appropriate controls) in a more masculine direction. They show more aggression (Berenbaum and Resnick, 1997b) or at least more masculinized forms of aggression (Hellday et al., 1993b), and more masculine-related social behavior and activity levels (Dittmann et al., 1990c,b). They express less interest in infants and in maternal behavior have lower empathy than controls (Cohen-Bendahan et al., 2005a). Cognitively they score higher than unaffected girls on spatial visualization and spatial orientation, two variables with an established sex difference (Berenbaum et al., 2012; Cohen-Bendahan et al., 2005a). Finally, they also have a higher frequency of same-sex orientation than their female peers (Cohen-Bendahan et al., 2005b; Dittmann et al., 1992a; Zucker et al., 1996a).

However, CAH girls are far from being boys in girls’ bodies. In all of the phenotypes, CAH girls have means between control girls (or women) and males. For example, over 70% of CAH women have a heterosexual orientation.

One of the most intriguing facts to emerge from the CAH literature is that the largest difference between the CAH girls and unaffected controls is on interest patterns (Cohen-Bendahan et al., 2005a). Most psychologists had thought that interests would be highly malleable since there have been marked secular trends over the 20th century in women’s vocational aspirations in, say, medicine and law. Why interest patterns differ more than personality traits like aggression or cognitive traits like spatial visualization remains an intriguing mystery.

CAH illustrates how a Mendelian trait can be used as a quasi-experiment to examine hormonal influences on behavior. Like all work on substantive human behaviors, the CAH story is not a clean and neat laboratory experiment and there are important confounding factors. Virilized girls undergo surgery and many also have hormone replacement therapy to counter the effects of low cortisol levels. Still the data on virilized CAH girls agree with the experimental manipulation of prenatal hormones in birds, rodents, and primates. There appears to be a sensitive period during which hormones exert an influence on later
sex-typed behaviors. How prenatal hormones do this work is a topic of intense research.

7.5 Aldehyde Dehydrogenase-2 deficiency

After alcohol is ingested, it enters the stomach and small intestine where it is absorbed into the bloodstream and carried throughout the body. The major organ that metabolizes alcohol is the liver. Here, alcohol is converted into acetaldehyde by the enzyme alcohol dehydrogenase (ADH), and acetaldehyde is then converted into acetic acid by the enzyme aldehyde dehydrogenase or ALDH (see Figure 7.5). There are several genes that have blueprints for ALDH, each of which makes different forms of this enzyme in different tissues of the body. One gene, ALDH2, codes for the major form of this enzyme located in liver mitochondria where most ingested alcohol is metabolized.

When a person has ALDH-2 deficiency, then the acetaldehyde cannot be readily converted into acetic acid and acetaldehyde builds up in the system. The amount of build up depends, of course, on the amount of alcohol ingested and the time course of ingestion. When the build up of acetaldehyde is rapid, the person may show the symptoms of a “flushing” response in which the person’s face turns red. (The reason is peripheral vasodilation. The blood vessels in the periphery become enlarged and carry more red blood).

In addition to flushing, excess acetaldehyde may cause some unpleasant effects, notably dizziness and nausea. Disulfiram (Antabuse®) produces a similar reaction because it inhibits the ALDH enzyme.

Many individuals with ALDH2 deficiency develop mild conditioned food aversions to alcohol while others reduce the amount of drinking to avoid the unpleasant symptoms. Because these individuals abstain or are temperate drinkers, the risk for developing alcohol abuse and alcohol dependence is reduced. Consequently, when individuals with this allele drink alcohol, the pathway from acetaldehyde to acetic acid is blocked (or greatly diminished in activity), and acetaldehyde accumulates in the blood and tissue.

Both the ALDH2 allele and the flushing response are associated with alcohol metabolism and elimination (Steinmetz et al., 1997; Yin, 1994), drinking habits (Higuchi et al., 1996; Nakawatase et al., 1993; Muramatsu et al., 1995; Tu and Israel, 1995), alcoholism (Murayama et al., 1998; Thomasson et al., 1991; Yoshida, 1992), and alcoholic liver diseases (Tanaka et al., 1997; Yoshida, 1992). Individuals with this allele are more often abstainers or, those who do
drink imbibe lower quantities of alcohol and engage in less binge drinking than those without the allele (Tu and Israel, 1995). Thus, the allele appears to lower the risk for the development of alcohol-related problems.

As many as 50% of Orientals possess an allele at the ALDH2 locus that results in an ALDH2 enzyme molecule that has either greatly reduced activity or no activity at all (Goedde et al., 1983; Yoshida, 1992). Because the allele is present among different Asian populations, but is either missing or extremely rare among Caucasoids and Africans, it has been postulated as one of the factors that contribute to lower rates of drinking among Asians. Tu and Israel (1995) go so far as to claim that this gene is the major predictor of the difference in drinking habits between Asians and other ethnic groups in North America. The reason why the allele for ALDH2 deficiency is so high in some Asian groups is not understood.

The ALDH-2 polymorphism is a classic example of how a gene can influence behavior. The mechanism of its action can be traced all the way from the DNA to the substantive behavior. First, at the DNA level, a single nucleotide (an adenine replaces a guanine) substitution at the ALDH-2 locus results in an altered polypeptide chain in which lysine replaces the usual amino acid glutamate. To get the enzyme molecule, four of these polypeptide chains must be joined together. If a person is homozygous for the deficient allele, then all four polypeptide chains have the deficiency and the person has virtually no viable ALDH2 enzyme. These homozygotes can become alcoholic but at vastly reduced rates. Chen et al. (1999) report that they are 100 fold less likely to develop alcohol dependence than someone with two normal alleles.

For a heterozygote—one normal allele and one deficient allele—the only active ALDH enzyme molecules in the liver will occur when, by dumb luck, all four of the peptide chains from the good allele get joined together. The probability of this occurring is 1/16, so only 6% of the ALDH2 molecules in the heterozygote’s liver are capable of fully converting acetaldehyde to acetic acid. This is the likely reason why ALDH-2 deficiency shows some degree of dominance.

There are also other very important lessons from the ALDH-2 story. First, it has been repeatedly demonstrated that people with the deficiency can still become alcoholic. For example, Thomasson et al. (1991) report that 12% of Chinese alcoholics in Taipei were heterozygotes for this gene. Thus, the gene influences risk, but in the heterozygote, it does not guarantee a life free of alcohol problems. Many geneticists refer to this type of a locus as a major susceptibility gene or a major locus—depending upon background genotype and environmental factors, it increases or decreases the probability of alcohol problems but does not rigidly determine alcohol use.

Second, the enzyme defect does its work in the liver, not in the central nervous system. There is a natural tendency to suspect that genetic effects on behavior operate on development of the nervous system and on the enzymes and proteins responsible for communication among neurons. The ALDH-2 story is a sober reminder that genes operating elsewhere in the body can influence behavior. Could some forms of schizophrenia turn out to be liver disorders?
Figure 7.6: A sickled red blood cell among several normal, platelet-shaped red blood cells.

From: http://www.nature.com/scitable/topicpage/sickle-cell-anemia-a-look-at-global-8756219

7.6 Sickle cell disease

Sickle cell disease (SCD, aka sickle cell anemia) is a recessive disorder due to alleles that influence the β chain of the hemoglobin molecule. The sickle cell anemia allele is a point mutation (i.e., the substitution of just one nucleotide for another) that results in a different amino acid being substituted into the β polypeptide\(^2\).

The effect of this amino acid substitution is profound. After the hemoglobin molecule transfers the oxygen to the target organ, the hemoglobin molecules often line up in a side to side fashion to create a long thin string. The abnormal hemoglobin from the sickle cell allele causes these strings to form into rigid bundles that change the shape of the red blood cell from a platelet into an elongated form (Mirchev and Ferrone, 1997). Viewed under the microscope, the elongated red blood cells often resemble the blade of a sickle, giving the disorder its name (See Figure 7.6).

The altered shape of the red blood cells has two major consequences. First it makes it easier for them to be destroyed, contributing to anemia (low red blood cell count). Second, the sickled shape makes it much easier for the red blood cells to clog up the small capillaries. This impedes circulation and ultimately deprives target organs of blood and oxygen. If matters do not return to normal, the person can enter a "sickling crisis" in which she/he experiences profound weakness, pain, and cramps. The medical complications from the anemia and the slow necrosis (cell death) of the organs lead to early death. Although a minority of sufferers have a benign course (Thomas et al., 1997), a significant proportion of people with sickle cell anemia who lack access to modern medicine do not survive to adulthood (variable expressivity again). Like many lethal

\(^2\)There are actually two major alleles, denoted HbS add HbC that can cause the disease. The HbC allele, however, is rare so most texts focus on HbS.
genetic disorders, however, medical advances have increased both the length and quality of life of people with sickle cell anemia (Reed and Vichinsky, 1998; Sheth et al., 2013).

Apart from the medical symptoms, people with sickle cell anemia have normal behavior. They have the same prevalence of psychiatric disorders as members of the general community (Hilton et al., 1997). Intellect and cognitive functioning are normal, apart from the disruptive and momentary influence of a sickling crisis and the long term effects of medical complications such as infarcts (Armstrong et al., 1996). The major lesson from sickle cell anemia resides its population genetics and not in any behavioral sequelae of the syndrome.

In the past, it was known that the allele for sickle cell anemia was found in high frequency in areas of Africa, the Saudi Arabian peninsula, and the Indian subcontinent (see Figure 7.7). Originally, it was speculated that the mutation for sickle cell anemia originated several thousand years ago among the Bantu-speaking peoples of Africa and diffused to the other areas, but current evidence supports the idea that independent mutations occurred in the different geographical locales (Mears et al., 1981; Solomon and Bodmer, 1979; Wainscoat et al., 1983). At least four independent mutations occurred in Africa and one in the Saudi peninsula. Figure 7.8 shows the distribution of the major haplotypes for the sickle cell allele.\footnote{A haplotype is discussed in Section X.X. Here, it refers to the allele causing sickle cell disease and other alleles close to it.}

After the original mutations, the allele for SCD underwent a unique evolutionary history that corresponded to the presence or absence of a particular form of malaria (falciparum) in the differing ecologies. It turns out that heterozy-
Figure 7.8: Distribution of the major sickle cell alleles by origin.

From: http://www.nature.com/scitable/topicpage/sickle-cell-anemia-a-look-at-global-8756219
gote carriers (those with one normal and one sickle cell allele) were resistant to malaria, especially its lethal consequences such as cerebral malaria. In the heterozygote the red blood cells that carried the malarial parasite would tend to sickle themselves and be readily destroyed. This prevented the infection from running amok in a heterozygote and increased the survival rate.

Hence, the frequency of the allele among the various populations evolved as a function of a malarial ecology. In regions free of malaria, there was no advantage to the heterozygote, so the sickle cell allele diminished in frequency. Indeed, the allele is quite rare in many populations of eastern Africa, especially around the Horn, and southern Africa. In the Saudi peninsula, its prevalence is high in oasis populations where mosquitoes are encountered but quite rare among neighboring desert nomads (el Hazmi et al., 1996). In malarial regions, the allele encountered two opposing selective pressures—the lethality of the allele in the recessive homozygotes worked to remove it from the population but the advantage conferred by the allele to the heterozygote worked to increase its frequency. These two opposing forces eventually arrived at an equilibrium in which the frequency of the sickle cell allele remained much higher than it did in nonmalarial areas. To give some figures, the frequency of the sickle cell allele is .01 or less in some South African populations but exceeds .25 in some areas of western Africa where malaria could at times reach epidemic proportions.

The major lesson of sickle cell is the complex relationship between genes, race-ethnicity, and ecology. Somewhere between 5% and 9% of African-Americans carry the sickle cell allele, and in this country it is often perceived of as a "black" disorder (Lorey et al., 1996). There is an element of truth to this, but the mere association of a gene with what we socially define as race and ethnicity is a gross understatement compared to the rich biology behind sickle cell anemia. The statistical association that we observe is the visible part of an iceberg fashioned by millennia of environmental adaptation, ecology, evolutionary fitness, and a big dash of just dumb luck.

The first part of dumb luck is the multiple origins of the mutation. These origins could have just as well occurred in other malarial regions such as the Mediterranean or Southeast Asia, but they just happened to occur in Africa and Saudi Arabia. The second chance event was that the mutation was beneficial to some—but certainly not all—of the people who carried it. The reason that it increased in frequency had everything to do with the biology and the ecology of malaria and absolutely nothing to do with the external morphology that we use as cues to ethnicity. This is why it spread outside of Africa and from the Middle East into Asia.

The last piece of dumb luck is the location of the slave trade into the New World. The majority of embarkation ports were on the West and West-Central coast of Africa and a majority of victims came from the neighboring indigenous populations—precisely those areas where malaria occurred in high frequency and the sickle cell allele was most prevalent. Had the slave trade originated from ports in South Africa, we would never consider sickle cell anemia as an "African-American" disease. Had the slave trade originated in some parts of India instead of western Africa, we might consider it an "Indian-American"
It is time to reflect once again on the relationship between correlation and causality—correlations do not necessarily imply causality. The correlation or the statistical association, if you prefer that term, between sickle cell anemia and African-American heritage does not imply any direct causality between a section of DNA coding for hemoglobin and any index of African-Americans. The causes are dumb luck, evolution, and historical accident.

### 7.6.1 Discrimination and sickle cell disease

In the 1960s advances in genetic techniques permitted detection of heterozygotes or carriers of the sickle cell allele. At the same time, many geneticists urged governments to implement mandatory genetic testing at birth for conditions like phenylketonuria whose sufferers benefit from early detection and intervention. In the early 1970s, several health-care bills passed by the US earmarked funds for research into the detection and treatment of SCD along with public health education about the disorder. Many African-American leaders along with such diverse groups as the Black Panthers urged African-Americans planning to marry another African-American to have carrier testing. Such noble intentions, however, gave way to a distasteful reality.

The first problem was semantic. A heterozygote was said to have “sickle cell trait,” and there was widespread confusion, even within the medical community between “sickle cell trait” and “sickle cell disease” (Aspinwall, 2012; Wailoo, 2001). The second problem was the empirical fact that under conditions of oxygen deprivation, including those induced by strenuous exercise, many people with the disease would undergo a sickling crisis. Coupled with the semantic confusion, several industries demanded carrier testing for potential African-American applicants and prohibited employment upon a positive result. For example, the U.S. Air Force and many major airlines prohibited carriers as pilots or flight attendants (Aspinwall, 2012). The third problem was overt racism—employers demanded testing to avoid hiring African-Americans.

The consequence was enhanced discrimination against African Americans in education, insurance, and employment. This reinforced a sense of suspicion in the African-American community about public health efforts aimed at them. It took considerable time to overcome the scientific misunderstanding. It wasn’t until 1981, for example, that the U.S. Air Force Academy ended its policy of refusing admittance to sickle cell carriers (Severo, 1981).

It is true that some carriers may suffer adverse health consequences—even death—but the documented conditions are extreme. Examples include the physical exertion required during basic training in the Armed forces (Kark et al., 1987) and collegiate football practice (Harmon et al., 2012). The current medical recommendation is not to screen for sickle cell carriers. Instead, all individuals undergoing such strenuous activity should be provided with the proper hydration and rest to avoid problems. To put the matter in perspective, the relative risk for an unexplained death for a sickle cell carrier during basic training was 32 per 100,000. For some aged 26 to 30, however, the relative risk was 95 per
7.7 Conclusion

In this chapter we have learned about several mechanisms for disorders. Classic metabolic blocks cause phenylketonuria and congenital adrenal hyperplasia. In PKU, the deleterious alleles occur at a single locus (that for the enzyme phenylalanine hydroxylase) while for CAH, the faulty alleles could occur at five different loci. Errors in genetic regulation can also influence phenotypic irregularity—the abnormal methylation of the FMR-1 locus is responsible for the Fragile X syndrome.

Genes, however, can act as protective factors that diminish susceptibility towards disorders. The ALDH-2 polymorphism is a classic example because the presence of the less frequent allele diminishes the probability of alcohol abuse and alcohol dependence. This trait also illustrates one biochemical mechanism for genetic dominance (to be exact—partial dominance). The heterozygote will produce two types of mRNA that result in two types of translated polypeptide chains—one functional and the other nonfunctional. Because four of these polypeptide chains must join together to give the ALDH-2 enzyme, only 1 in 16 ALDH-2 molecules in the heterozygote will be functional.

Sickle cell disease illustrates how an allele can be beneficial in one circumstance (i.e., in the heterozygote) but harmful in another (the recessive homozygote). Hence, the influence of an allele or a gene must always be judged against the genetic background in which it occurs. Sickle cell also demonstrates how human genetic diversity can be caused by ecological factors giving secondary correlations with what we socially define as race and ethnicity. For all these traits, one cannot help but marvel at the degree of penetrance, pleiotropism, and variable expressivity when the phenotypes are "molar" behaviors such as cognitive ability, attentional processes, personality, and psychopathology.

It is very likely that the same principles may apply to the genes that underlie more common phenotypes. Perhaps a single gene may have a large effect on schizophrenia when it occurs along with a certain genetic background but only a small influence when present in another background. Any particular locus for, say, intelligence is bound to have considerable variable expressivity. And the effects of other loci may be to buffer an individual against developing agoraphobia.

7.8 References


