Chapter 5: Mendelian Traits and Behavior

Introduction

According to geneticists, a Mendelian trait is due to a single gene that follows classic Mendelian transmission. Likewise, a Mendelian disorder is one influenced by a single locus. In this chapter, we examine several Mendelian traits and disorders in order to illustrate the basic principles of how genes and gene products relate to behavior. The lessons will be broad. They begin with the genetic disorder of phenylketonuria that illustrates basic principles of metabolic pathways and conclude with sickle cell anemia, a disorder that illustrates the relationship between genes, ecology, and ethnicity. Before beginning, however, we must provide some terminology.

Introductory Terminology:

One does not inherit genes per se. Instead, at conception we all inherited several distinct strands of DNA that are "packaged" within a complex system of proteins. Hence, it is the *chromosome* and not the gene that is truly the physical unit of inheritance. A *gene* is usually defined as a section of DNA that contains the blueprint for a polypeptide chain. The term *locus* (plural = *loci*) is a synonym for gene; it carries with it the implication that a gene has a fixed location on a chromosome. A single human chromosome will contain several thousands of genes.

The term *allele* may be defined as a "spelling variation" at a gene, i.e., a difference in the positioning and ordering of the A, T, C and G nucleotides along that stretch of DNA. Unfortunately, many geneticists also use the term gene to refer to an

allele, sowing untold confusion among beginning genetics' students, so let us examine a specific case to explain the technical difference between a gene and an allele. The ABO gene (or ABO locus) is a stretch of DNA close to the bottom of human chromosome 9 that contains the blueprint for a protein that sits within the plasma membrane of red blood cells. Not all of us, however, have the identical sequence of A, T, G, and C nucleotides along this DNA sequence. There are spelling variations or alleles that exist in the human gene pool at the ABO locus. The three most common alleles are the A allele, the B allele, and the O allele.

Because we all inherit two number nine chromosomes—one from mom and the other from dad—we all have duplicate copies of the ABO locus. By chance, the spelling variation at the ABO stretch of DNA on dad's chromosome may be the same as the spelling variation at this region on mom's chromosome. An organism like this is called a *homozygote* (*homo* for "same" and *zygote* for "fertilized egg"). The strict definition of a homozygote is *an organism that has the same two alleles at a gene*. For the ABO locus, those who inherit two A alleles are homozygotes as are those who inherit two B alleles or two O alleles. A *heterozygote is an organism with different alleles at a locus*. For example, someone who inherits an A allele from mom but a B allele from dad is a heterozygote.

The *genotype* is defined as the genetic constitution of an individual. A genotype may refer to only one locus or it may refer in an abstract sense to many loci. At the ABO locus, the genotypes are AA, AB, AO, BB, BO, and OO. (There is a tacit understanding that the heterozygote AO and OA are the same genotype.)

A *phenotype* is defined as the *observed characteristic or trait*. Height, weight, extraversion, intelligence, interest in blood sports, memory, and shoe size are all phenotypes. *There is not always a simple, one-to-one correspondence between a genotype and a phenotype.* For example, there are four phenotypes at the ABO blood group—A, B, AB, and O. These phenotypes come about when a drop of blood is exposed to a chemical that reacts to the polypeptide chain produced from the A allele and then to another chemical that reacts specifically to the polypeptide chain produced from a B allele. (The O allele produces no polypeptide chain, so there is no reaction). If someone takes a drop of your blood, adds the A chemical to it, and observes a reaction, then it is clear that you must have at least one A allele—although, of course, you may actually have two A alleles. The person takes another drop of your blood, adds the B chemical, and observes a reaction, and then you must have phenotype AB. In this case, your genotype must also be AB. If a reaction occurs to the A chemical but not to the B chemical, then you have phenotype A but could be genotype AA or genotype AO—the test cannot distinguish one of these genotypes from the other. Similarly, if your blood fails to react to the A chemical but reacts to the B chemical, then you are phenotype B, although it is uncertain whether your genotype is BB or BO. When there is no reaction to either the A or the B chemical, and then the phenotype is O and the genotype is OO.

Finally, there are several terms used to describe allele action in terms of the phenotype that is observed in a heterozygote. When the phenotype of a heterozygote is the same as the phenotype of one of the two homozygotes, then the allele in the homozygote is said to be *dominant* and the allele that is "not observed" is termed *recessive*. Because the heterozygote with the genotype AO has the same phenotype as

the homozygote AA, then allele A is dominant and O is recessive. Similarly, allele B is

dominant to O, or in different words, allele O is recessive to B. When the phenotype of

the heterozygote takes on a value somewhere between the two homozygotes, then allele

action is said to be *partially dominant*, *incompletely dominant*, *additive*, or *codominant*,

depending on exact value of the heterozygote. Because the genotype AB gives a

different phenotype from both genotypes AA and BB, one would say that alleles A and B

are codominant with respect to each other. (The term *additive* would equally apply, but

this phrase is usually used when the phenotypes are numbers and not qualities.) Note

carefully that allele action is a *relative* and not an *absolute* concept. For example, the

allele action of A depends entirely on the other allele—i t is dominant to O but

codominant to B.

Introduction: Relationship between genotypes and phenotypes.

Let us now examine three central terms that describe the relationship between a

single gene and a phenotype. The first of these is *penetrance*. 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, 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[1]. *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. Not everyone with the dominant gene for Marfan's develops 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—intellect 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[2]. 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 *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

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[1] You may have noted the cautionary phrases "close to 1.0" and "almost always develop the disorder." In the past cystic fibrosis (CF) was regarded as having a penetrance of 1.0, but with the advent of genotyping at the locus, several cases were discovered that had the genotype for CF but did not show the complete syndrome.

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.

Phenylketonuria (PKU)

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; mental retardation; irritability; and hyperactivity.

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*) arm of chromosome 12. Part of the metabolic pathway that involves this enzyme is depicted in Figure 5.1. Let us spend some time going through this figure so that we can learn about the pathways from gene to behavior.

[Insert Figure 5.1 about here]

Phenylalanine is an amino acid and, hence, a necessary constituent of peptides, proteins, and enzymes. The two major sources of phenlyalanine are diet and the

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[2] Some people with HD develop a rigid, akinetic (i.e., absence of movement) form.

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. The enzyme PAH is responsible for the second of these—the

conversion of phenylalanine into tyrosine. When PAH is defective, then it acts as a

metabolic block[3]. 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.

At this stage, let us postpone discussion of the metabolic pathway to focus on the

first 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 the US 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

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[3] The term metabolic block is very important in genetics and describes a mechanism for a large number of Mendelian disorders. Generically, it refers to a defective enzyme that results in the buildup of precursor substances in a metabolic pathway.

standard formula, and after weaning, must avoid all foods with high levels of protein and be maintained on special dietary supplements[4].

If the diet is adhered to, then the mean IQ of children with PKU does not differ markedly from normals. Many finer issues about the diet are still debated—e.g., the levels of blood phenylalanine that are considered safe [Diamond, 1994 #117]; the age at which the diet may be discontinued [Azen, 1996 #37; Burgard, 1996 #36; Griffiths, 1995 #112]; and the importance of supplementing the diet with tyrosine [Diamond, 1996 #116][5]. 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.

We can now return to the metabolic pathway. Because the enzyme PAH is damaged, the amount of tyrosine is reduced in PKU[6]. 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 #116].

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[4] 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.

[5] In some cases, dietary restrictions may be continued throughout life. Another special case involves women with PKU who desire to have children; to avoid damage to the fetus, they are urged to go on a phenylalanine restricted diet before conception.

We have now encountered the second major lesson that PKU has for the genetics of behavior—*pleiotropism* or the phenomenon of a single gene influencing 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 Figure 5.1 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 5.1—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 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

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[6] For example, tyrosine is often added to the diet of PKU children.

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.

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 blocks; hence

as a general rule, the mRNA transcripts and the translated enzymes from only one DNA

segment (i.e., allele) is sufficient to maintain metabolism.

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. Well

over a hundred different alleles at the PAH locus have been identified; if any two of these

hundred or so alleles come together, then PKU will result. Because there are so many

different alleles, most people with PKU do not have the same nucleotide sequence at both

of their PAH genes. Again, there is an active research examining the correlation between

the genotype and the phenotypic consequences from this allelic variation [Ramus, 1993

#39; Koch, 1997 #58; Trefz, 1993 #69].

The fourth lesson from PKU comes from examining the IQ distribution in untreated cases, presented in Figure 5.2[7]. Figure 5.2 presents the IQ distribution of

[Insert Figure 5.2 about here]

[this section has not been written yet]

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia[8] (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. Figure 5.3 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. Because CAH is genetically heterogeneous, a block at any one of the five enzymes listed in Figure 5.3 will result in the syndrome.

[Insert Figure 5.3 about here]

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[7] Here, we must go back several generations to examine the relevant data. Virtually all PKU cases in countries with active medical research programs are now detected at birth and treated soon after. Hence, untreated cases are, thankfully, a rarity.

[8] Hyperplasia refers to an abnormal number of cells in a tissue, organ, etc. Hence, CAH is the name for a congenital syndrome involving an abnormal number of cells in the adrenal glands located on the top of the kidneys.

CAH also influences sexual differentiation. The adrenal gland plays an important part in the early masculinization of the fetus before the testes are fully developed. Not only is cholesterol the precursor to cortisol, but it is also a precursor to the important androgen[9] testosterone (see Figure 5.3). When the metabolic block occurs after the branch point between androgen production and the synthesis of 17-hydroxyprogesterone, then there is a build up of the precursors to testosterone and the fetus can be masculinized, even when the fetus has two X chromosomes. When the metabolic block occurs before this branch, there is little precursor to testosterone, so the fetus will not undergo normal sexual development[10].

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. Initial sex development proceeds normally, so the tissues develop into the usual internal sex organs—ovaries, fallopian tubes, etc. However, the high dose of male hormones alters the development of the external genitalia toward a male direction. 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

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[9] An *androgen* is a class of hormones that masculinizes a fetus.
[10] In these cases CAH can also influence estrogen levels and sexual development in XX individuals.

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, 1992 #29], 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 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. This suggests that the extra prenatal androgen does not "super masculinize" a boy, at least with respect to toy preferences. The CAH girls, on the other hand, exhibited a preference that resembled the control boys more than the control girls. Berenbaum and Himes 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 show more aggression [Berenbaum, 1997 #1] or at least more masculinized forms of aggression [Helleday, 1993 #8] than their normal sisters and cousins. They often show more masculine-related social behavior and activity levels [Dittmann, 1990 #11; Dittmann, 1990 #12]. However, CAH girls are far from being boys in girls' bodies. Although their psychosexual orientation differs slightly from that of normal girls and women, [Dittmann, 1992 #9; Zucker, 1996 #4] report that as a group they are heterosexually oriented and well adjusted.

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.

Aldehyde Dehydrogenase, Alcohol Use, and Alcohol Abuse

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 5.4). 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.

[Insert Figure 5.4 about here]

As many as 50% of Orientals posses an allele at the ALDH2 locus[11] that results in

an ALDH2 enzyme molecule that has either greatly reduced activity or no activity at all

[Goedde, 1983 #41; Yoshida, 1992 #33]. 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. The result

is often a "flushing" response in which the person may turn red and experience

uncomfortable side effects such dizziness and nausea. Disulfram (Antabuse) produces a

similar reaction because it inhibits the same enzyme.

Both the ALDH2 allele and the flushing response are associated with alcohol

metabolism and elimination [Steinmetz, 1997 #20; Yin, 1994 #14], drinking habits [Tu,

1995 #25; Takeshita, 1998 #17; Nakawatase, 1993 #28; Muramatsu, 1995 #24; Higuchi,

1996 #22], alcoholism [Murayama, 1998 #16; Thomasson, 1991 #32; Yoshida, 1992

#33], and alcoholic liver diseases [Tanaka, 1997 #19; Yoshida, 1992 #33]. 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 & Israel,

1995). Thus, the allele appears to lower the risk for the development of alcohol-related

problems.

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, and hence, lowered rates for alcohol abuse and dependence among Orientals. 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 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 substitution at the ALDH-2 locus results in an altered polypeptide chain[12]. Four of these chains are joined together to get this form of the ALDH enzyme. If a person has one normal allele and one deficient allele, then the only active ALDH enzyme molecules in the person's liver will occur when, by dumb luck, four of the peptide chains from the good allele get joined together. This is the likely reason why ALDH-2 deficiency shows some degree of dominance[13].

When a person drinks alcohol, the enzyme ADH converts the alcohol into acetaldehyde. When that person has ALDH-2 deficiency, then the acetaldehyde cannot be readily converted into acetic acid and 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 occurs, the person may show the symptoms of a

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[11] The allele causing the deficiency is called the ALDH2*2 allele; ALDH2*1 is the normal allele.

[12] The normal codon for the 487th amino acid in the polypeptide chain is GAA which codes for glutamic acid; in the ALDH-2 deficiency, an A replaces the G giving the codon AAA which places a lysine into the polypeptide sequence.

[13] At this date, there have been no reported cases of alcoholism among homozygotes for the deficient ALDH-2 allele. Because heterozygotes have a reduced rate of alcoholism, the gene action of the locus is codominant.

flushing response. The response and its severity vary from one person to another, but in some individuals it is associated with unpleasant effects. Many of these individuals may 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.

There are also other very important lessons from the ALDH-2 story. First, it has been repeatedly demonstrated that heterozygotes can still become alcoholic. For example, [Thomasson, 1991 #32] 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 *susceptibility* gene—depending upon genotype, 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?

Fragile X Syndrome

In contrast to most clinical presentations, let us first consider the genetics of the Fragile X syndrome[14] and then discuss its clinical manifestations. The gene responsible for the syndrome is called the FMR-1 locus and is located on the X chromosome. The complete role of the FMR-1 protein is still not unclear, but it is well established that the protein binds with RNA and may play a role in the functioning of ribosomes. The genetic problem causing Fragile X is *an abnormal number of trinucleotide repeats* inside the FMR-1 gene. Within the area of the DNA that is initially transcribed from this gene, all humans have a series of CGG repeats. Normally, the number of CGG repeats ranges between 6 and 50. However, when the number of CGG repeats reaches a critical value (usually taken as 200), the DNA becomes methylated, transcription of the gene is inhibited, levels of the FMR-1 protein decline, and some form of Fragile X results. The degree of impairment in Fragile X is correlated with the number of CGG repeats—the larger the number, the greater the impairment.

To recapitulate, 6 to 50 CGG repeats is normal but 200 or more repeats is associated with pathology. What about repeats in the 50 to 200 range? Within this range, a curious phenomenon occurs. Individuals who carry 50 to 200 repeats are phenotypically within normal limits, but when they transmit the gene, it stands a higher probability of mutating to a greater length (i.e., it is *hypermutable*). Hence, individuals with 50 to 200 CGG repeats stand a high risk of transmitting an FMR-1 allele with more than 200 repeats to their offspring. This creates a phenomenon known as *anticipation*—an

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[14] Fragile X is so named because it was first described by cytogeneticists who noted that the X chromosome appeared to almost or completely break apart at a particular location in certain karyotype preparations. The localization of the disorder to a specific locus occurred after the syndrome was described.

increase in the clinical severity of a syndrome in more recent generations of the pedigree. As the gene travels "down" in a pedigree, it has tendency to elongate the repeat even further, thus creating more severe cases of Fragile X.

Because males have only one X chromosome, inheritance of a single abnormal allele will create some impairment in men. The vast majority of females who carry the abnormal allele are heterozygotes. Here, the allele action may be described as having incomplete penetrance or incomplete dominance because about half of these females will show measurable impairment, albeit quite minor impairment in a significant number of cases. The rare homozygous female can exhibit the same syndrome as a male.

The number of CGG repeats and the concomitant loss of FMR-1 protein influences several different phenotypes, illustrating once again the phenomenon of pleiotropy. As children, the physical features of Fragile X males blend well into the normal distribution, but at maturity they often develop elongated faces, large and protuberant ears, prominent foreheads and jaws, and enlarged testicles (macroorchidism). Often the development of connective tissue is influenced, giving Fragile X individuals double-jointed fingers and toes. Cognition and cognitive abilities are also affected. A significant number of Fragile X cases exhibit enough difficulties with concentration and attention and a sufficient number of hyperactivity problems to qualify for a diagnosis of Attention Deficit-Hyperactivity Disorder or ADHD. As a group, Fragile X individuals have low scores on IQ tests. However, the range of IQ scores is quite broad with many cases scoring in the low-normal range while others suffer from significant mental retardation. Indeed, Fragile X syndrome is the most frequent Mendelian disorder associated with mental retardation. Severe cases may also shows signs and symptoms

similar to those of autism—poor eye contact, failure to attend to social cures, and a general lack of responsiveness to human interaction—although the extent to which these behavior represent classic autism is a matter of debate. Irregularities in language development, speech patterns, cognitive styles, and mood have also been noted.

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.

Figure 5.5 presents a hypothetical pedigree that illustrates both the genetics 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.

[Insert Figure 5.5 about here]

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 a high probability of mutating to a longer series of repeats. A mutation occurs 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 her other normal 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 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 as mildly mentally retarded, 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 unarticulable 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.

Fragile X has many lessons for behavior. It has a great similarity to classic

"metabolic blocks" that act as a dam misplaced in the flow of a mountain stream so that

water backs up and floods surrounding areas. In the classic metabolic blocks such as

PKU and CAH, the problem is in the genetic blueprint for a protein or enzyme. In

Fragile X, however, the blueprint for the FMR-1 protein is perfectly fine. The defect is in

the *regulation of the protein's production*. The abnormal number of CGG repeats

effectively "turns the FMR-1 gene off," and the lack of gene product plays havoc within

the cell. Hence, we must always be alert to the possibility that various proteins, enzymes,

receptors, transporters, etc. might be perfectly normal in a disorder such as schizophrenia;

instead, it may be the timing of production and the amount of such proteins, enzymes,

etc., that could lead to psychopathology.

A second lesson from Fragile X is the mechanism of an abnormal number of

trinucleotide repeats. This is not unique to Fragile X. Indeed, an abnormal number of

CGG repeats at various loci is responsible for several Mendelian disorders, most notably

Huntington's disease. The fact has lead to research that is now searching for

trinucleotide repeats in schizophrenia, bipolar disorder, and other forms of

psychopathology. It is much too early to assess the merit of these approaches, but the

efforts may uncover a major model for some complex disorders associated with behavior.

Finally, the variable expressivity of Fragile X convincingly demonstrates the

futility of a "one-size-fits-all" approach to the clinical management of some genetic

disorders. Although there is no cure for Fragile X, various combinations of

pharmacotherapy (i.e., drugs), educational regimens, behavioral and cognitive therapy

can improve the day-to-day functioning of individuals with the syndrome. The precise

combination of these therapeutic techniques depends on the idiosyncratic expression of

signs and symptoms in the individual case. As is the case with many behavioral

problems, the optimal combination of therapies for Fragile X is determined more by

rational guesswork and clinical experience than by empirical research results.

Sickle Cell Anemia

Sickle cell disease is a recessive disorder due to alleles that influence the β chain

of the hemoglobin molecule. Several different alleles at the β hemoglobin locus can

cause sickle cell disease, but the most common allele in US populations causes *sickle cell*

anemia. 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[15].

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[15] The point mutation for sickle cell anemia occurs in the sixth codon of the chain. The normal DNA
codon is CTC that places the amino acid glutamate in the peptide chain. The allele for sickle cell anemia
substitutes adenine for thymine giving the DNA codon CAC that results in the amino acid valine being
placed into the chain instead of glutamate.

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, 1997 #134]. Viewed under the microscope, the elongated red blood cells often resemble the blade of a sickle, giving the disorder its name.

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 sickle 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, 1997 #127], most people with sickle cell anemia do not survive until adulthood (variable expressivity again). Like many lethal genetic disorders, however, medical advances are increasing both the length and quality of life of people with sickle cell anemia [Reed, 1998 #121].

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, 1997 #128]. 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, 1996 #131]. 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. 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 [Solomon, 1979 #118; Wainscoat, 1983 #119; Mears, 1981 #120]. At least three independent mutations occurred in Africa and one in India.

After the original mutations, the allele for sickle cell anemia underwent a unique evolutionary history that corresponded to the presence or absence of a particular form of malaria[16] in the differing ecologies. It turns out that heterozygote 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 her 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,

1996 #132]. 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.[17].

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,

1996 #133]. 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[18], but they just happened to occur in Africa and in India. The second

instance of chance is that the mutation was beneficial to somee—but certainly not all—of

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[16] *Plasmodium falciparum.*
[17] As might be expected, the ability to medically manage malaria along with its eradication in some areas
has resulted in a decrease in the frequency of the sickle cell allele.
[18] Instead, other genetic mutations occurred in these regions and increased in frequency because they
protected against the harmful effects of malaria. The mutations are the β thallasemia allele in the
Mediterranean area and the hemoglobin E allele in Southeast Asia.

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 into the Middle East and 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" disease.

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-Americaness. The causes are dumb luck, evolution, and historical accident.

Conclusions

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 anemia 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

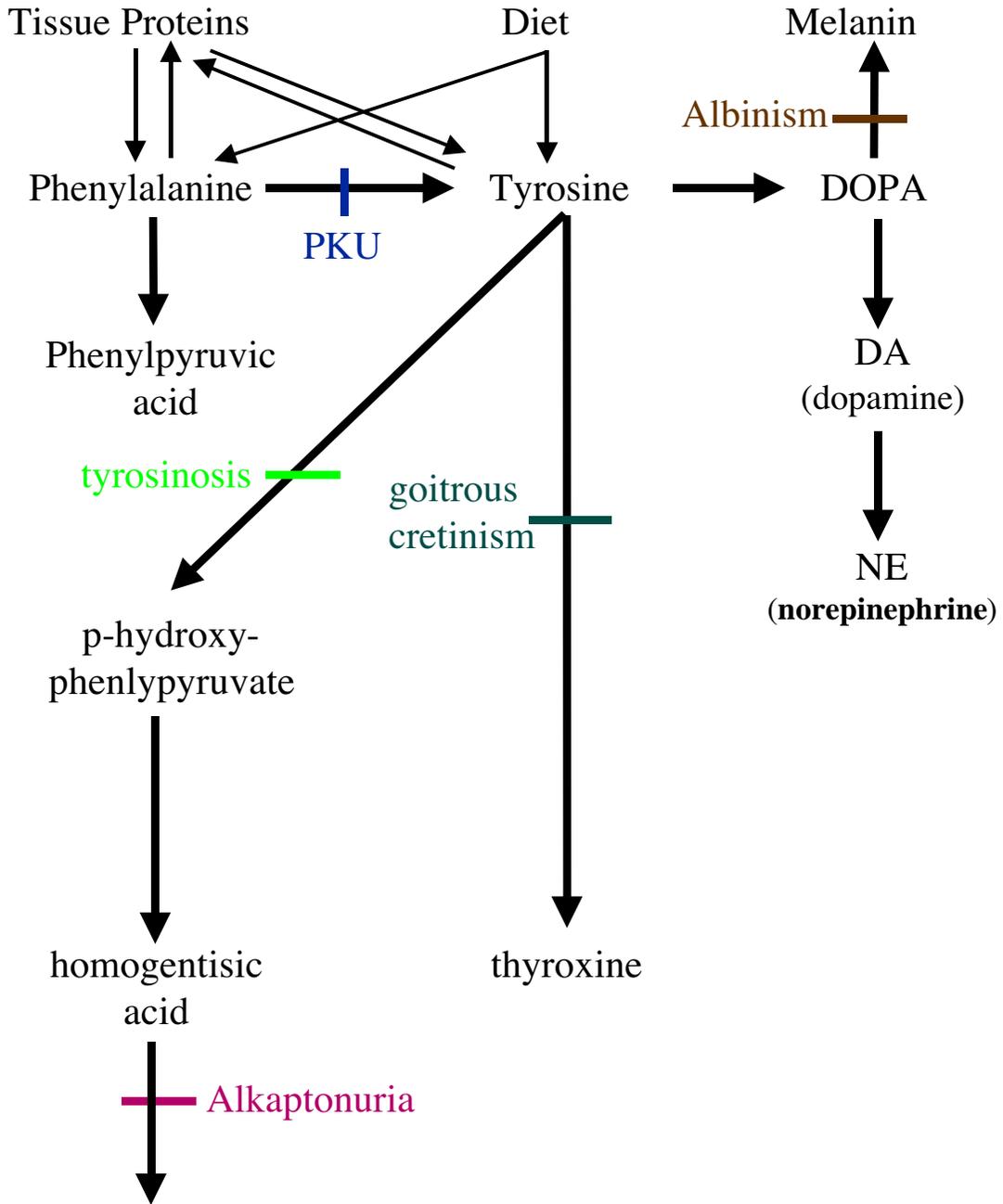individual against developing agoraphobia.

Tissue Proteins   Diet   Melanin

Albinism

Phenylalanine ⟶ Tyrosine ⟶ DOPA

PKU

Phenylpyruvic
acid

DA
(dopamine)

tyrosinosis

goitrous
cretinism

NE
(**norepinephrine**)

p-hydroxy-
phenlypyruvate

homogentisic
acid   thyroxine

Alkaptonuria

Figure 5.1. The metabolic pathway from phenylalanine to tyrosine. Metabolic blocks at a number of steps can produce disorders.

[waiting on the IQ Figure]

Figure 5.2. Waiting on the arrival of data to construct this figure.

Cholesterol

desmolase

Ambiguous, **no androgens**, **salt-wasting**

Pregnenolone

17-a-hydroxylase

Ambiguous, **low androgens**, **hypertension**

17-Hydroxy-pregnenalone → → **Androgens**

3-b-OH-dehydrogenase

Virilized, **high androgens**, **lethal**

17-Hydroxy-progesterone

21-hydroxylase

Virilized, **high androgens**, **salt-wasting**

11-Deoxycortisol

11-b-hydroxylase

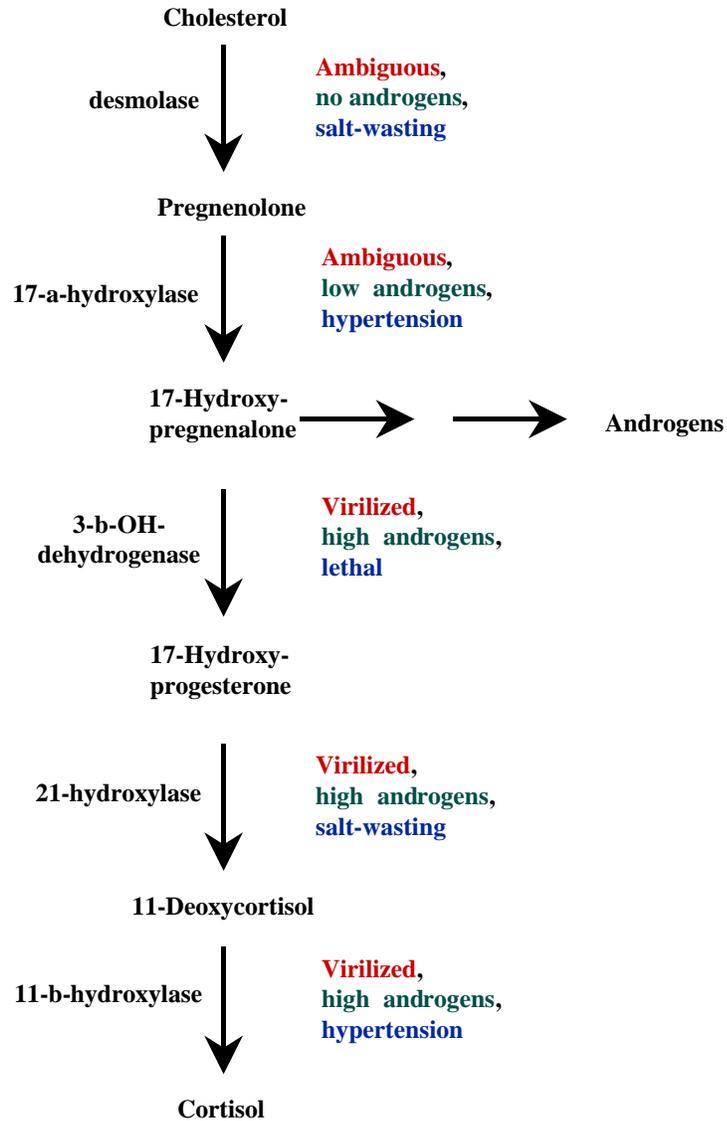**Virilized**, **high androgens**, **hypertension**

Cortisol

Figure 5.3. The metabolic pathway for the synthesis of cortisol from cholesterol. Metabolic blocks at any one of these steps can produce a form of congenital adrenal hyperplasia (CAH). Shown to the right of the metabolic step are the aberrations in the genitalia, androgen level, and major medical complications of the syndrome.

Alcohol → **Acetaldehyde** → **Acetic Acid**

Alcohol Dehydrogenase (ADH)
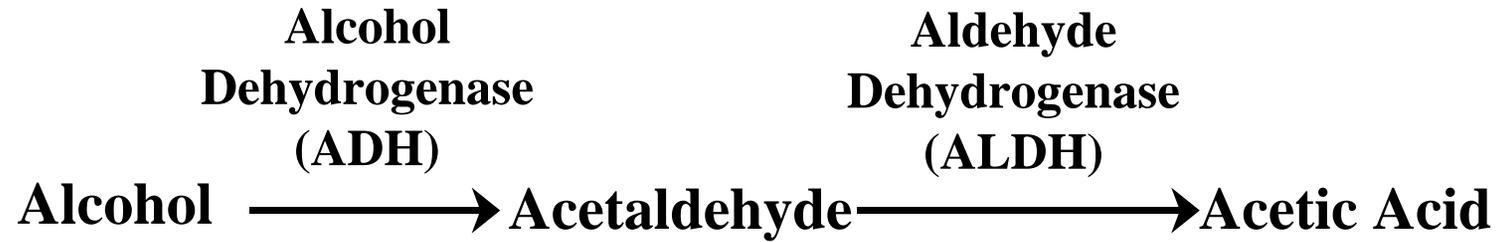
Aldehyde Dehydrogenase (ALDH)

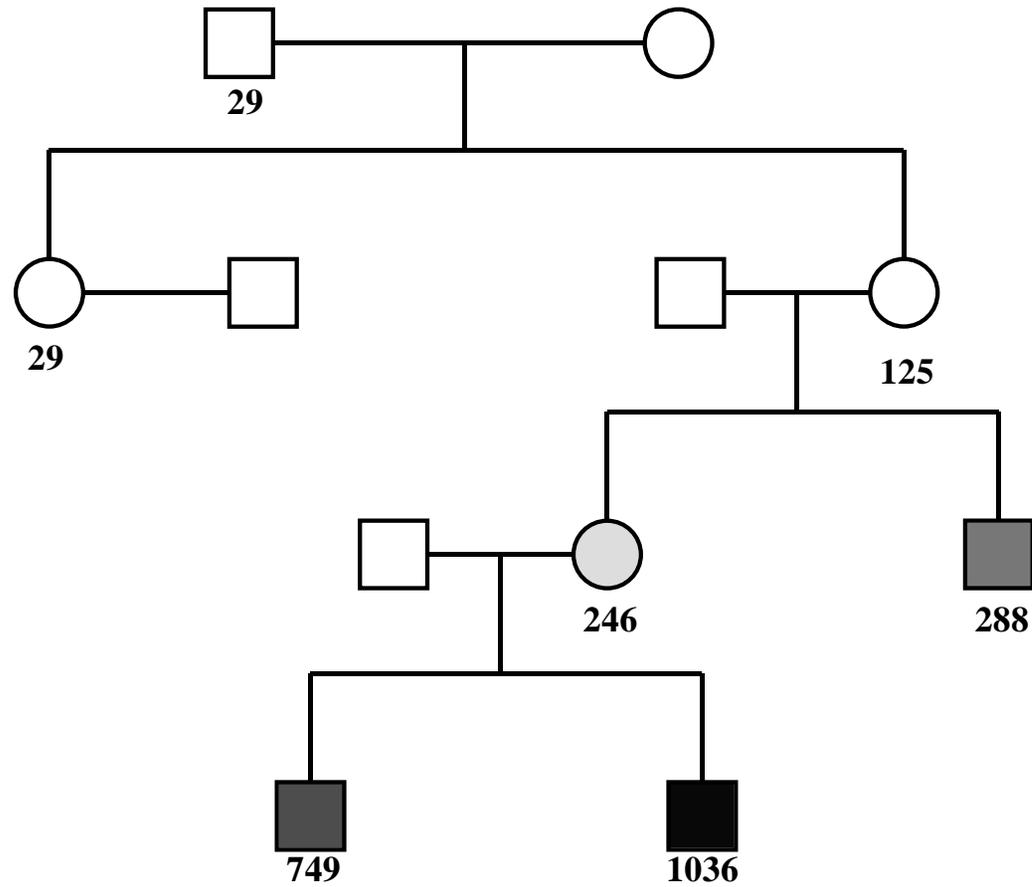Figure 5.4. The major pathway for the metabolism of alcohol in the liver.

Figure 5.4. A pedigree illustrating anticipation for Fragile X syndrome. The numbers below an individual give the number of trinucleotide repeats and the shading shows the degree to which the phenotype is affected.