

Chapter 6: DCG—Disorders with Complex Genetics

Introduction: Complex genetic disorders and disorders with complex genetics

In medicine and medical genetics, one often encounters the phrase *complex genetic disorder* to refer to many common syndromes like diabetes, cancers, and hypertension. The definition of a complex genetic disorder is quite simple—it is a disorder that has something genetic going on behind it but no one has a clue as to what the genetics are. The term complex genetic disorder is actually a misnomer because it implies that the disorder is genetic whereas empirical research usually shows that the environment can play a large etiological role. To insure that we do not neglect the environment, the term *disorder(s) with complex genetics* (DCG) will be used.

One central epidemiological variable correlates very highly with DCG—the prevalence of the disorder. The frequency of the most common Mendelian disorders is one in several thousands of births. The frequency of DCG is one to two orders of magnitude higher. Indeed, if a disorder has prevalence of .1% or above, it is certain to be a DCG.

In terms of human behavior, all forms of psychopathology (schizophrenia, affective disorder, the anxiety disorders, etc.) are disorders with complex genetics. Indeed, all forms of psychopathology have important—albeit largely unknown—environmental factors intimately tied up in their etiologies.

Do let the term DCG engender pessimism about ever finding the causes and effective treatments for psychopathology (or any medical DCG for that matter). Indeed, research into DCG, although it is very difficult, is one of the exciting challenges to both the genetic and the epidemiological community. Finding and cloning the gene for a Mendelian disorder is much akin to following the Oregon trail after a generation of pioneers have charted the land and founded communities along the way—just follow the road signs and you will get there. Research into DCG is like exploring virgin territory.

Alzheimer's Disease: A Model DCG

There are many model DCG—breast cancer, diabetes, hypercholesterolemia, atherosclerosis. Unfortunately, no forms of psychopathology can be used as a model DCG because our knowledge about their genetics is too embryonic at this stage. Perhaps the best model with behavioral sequelae is Alzheimer's disease (AD), so we will use that to illustrate how DCG is being researched.

AD: The Phenotype

AD is a progressive and irreversible disorder that involves damage and the eventual death of neurons in the central nervous system. The first sign of AD is usually memory loss for recent events—one may have trouble recalling the name of the current President but have no difficulty remembering who the President was when one was born.

In normals, memory abilities begin a slow decline starting in the mid 20s¹ and becoming noticeable in middle age—that familiar experience of visualizing a face but failing to recall the name just becomes more common with age. Indeed, it is quite difficult to distinguish the very early stages of AD from normal forgetfulness, and many family members fail to recognize that someone is having significant problems with memory.

As AD progresses, cognitive functioning and judgment deteriorate into dementia. It is not uncommon at this stage to see changes in personality—someone with a lifelong tendency to be patient and forbearing may become hostile and irritable or a reserved person may become outgoing and fatuous. Depression is also encountered. Eventually, all forms of reasoning are impaired, the person becomes unable to perform routine tasks like getting washed and dressed, and in the last stages is incapable of communication. The course of the illness can range anywhere between two and twenty years, but on average people with AD survive around 8 to 10 years after the first diagnosis. AD does not appear to be lethal per se. Instead, in the final stages, people become bedridden and physically weak, permitting opportunistic infections to occur. Most people with AD die from pneumonia.

AD is an adult disorder with an age of onset that can start as early as 30 to 40. The risk for developing AD increases with age and roughly doubles every 5 years after the age of 65. Advances in medicine and public recognition of healthy diets and lifestyles have dramatically increased life expectancy over the past century, greatly increasing the

¹ The decline in the 20s can be documented with psychometric tests but is virtually imperceptible and has

overall prevalence of AD, placing heavy economic burdens on the health care system, and creating heavy personal, emotional, and financial problems for family members and caregivers. For these reasons, AD is being heavily researched.

Although AD can be diagnosed using psychometric tests of memory and cognition, the only sure diagnosis is made on autopsy when the brain is examined under the microscope. AD brains show characteristic plaques and neurofibrillary tangles. Plaques are dense deposits of protein (especially beta-amyloid²) and non-nerve cells that build up outside the neuron. Neurofibrillary tangles occur when the neurofibers³ lose their structure and twist together.

AD is classified along two different dimensions—family history and age of onset. It has long been recognized that AD can run in some families, and early family studies suggested that a minority of families had transmission patterns consistent with a dominant gene. Today, family history is used to classify AD into two types, although the boundary between the two types is often quite fuzzy. The first type is called *familial Alzheimer's disease* or FAD and is diagnosed when the pedigree is consistent with dominant transmission. The second and by far more common type is usually

no practical consequences.

² Amyloid is a generic name for proteins or protein fragments that aggregate together and form an insoluble mass.

³ Neurofibers are long, thin, threadlike bodies that give structure to the neuron and act as transportation highways for neuronal chemicals.

referred to as *nonfamilial AD* or *sporadic Alzheimer's disease* and is diagnosed when there is no clear pattern of familial transmission⁴.

Although age of onset is a continuous and quantitative variable, it is often dichotomized giving the two classes of *early-onset AD* and *late-onset AD*. The age of onset distinguishing the two is usually taken as 60 to 65. The vast majority of AD patients are late-onset cases.

Familial Alzheimer's disease is strongly correlated with age of onset. Most FAD cases are early onset and also have a quickly deteriorating course. However, not all early-onset cases are FAD. Most late-onset cases are sporadic.

AD: Genetics of Familial Alzheimer's Disease

The fact that cases of Down's syndrome (which involves the inheritance of extra material from chromosome 21) eventually show the AD-like pathology of plaques and tangles focused early linkage and association studies on chromosome 21. Soon it was found that a small minority of FAD cases was due to mutations in the gene for the amyloid precursor protein (APP) on this chromosome. Shortly afterwards, other positive linkage results were found to a gene on chromosome 14. The gene has since been located and is called the presenilin 1 locus. Recently a third locus on chromosome 1, the presenilin 2 gene, has been implicated in AD in a group of German pedigrees originating from the Volga Valley in Russia.

⁴ In classical genetics, the term sporadic refers to a person with a Mendelian disorder (or more generally, a person with a certain Mendelizing phenotype) that appears unexpectedly in an otherwise normal pedigree.

The three loci—APP and presenilins 1 and 2—all show dominant transmission, so the risk to an offspring is .50. Together, they account for almost half of the families with FAD. But because FAD accounts for no more than 10% of all Alzheimer's cases, the three genes are responsible for roughly 5% of all AD. This is an important lesson from AD and is an emerging pattern in the study of DCG—Mendelizing forms occur, but they are rare and account for only a few percent of all cases⁵.

A second lesson—actually, a problem—from AD is the possibility of predicting who will develop a Mendelizing form of AD. A person with AD in a pedigree for FAD could be tested to find if s/he has a deleterious locus at one of the three genes. Under current medical genetic practice, decisions about whether or not to test reside with the patient. Nevertheless, thorny ethical issues emerge. Suppose that the grandfather in an FAD pedigree tests positive for the presenilin 1 mutation, but his son Fred and his granddaughter Sally are unaffected. Fred is very adamant that he not be tested or given any other information about whether he carries the gene. Sally, on the other hand, is equally adamant about being tested so that she can plan her life according to the results. If Sally is tested and tests negative, there is no problem—the probability that her father Fred has the gene remains at .50. However, if Sally tests positive, then Fred must have the gene because that is the only way Sally could have gotten it. If Sally's test results in this case become known within the family, Fred's decision to remain uninformed is

Sporadics may be due to new mutations, to environmental factors, or to some complex interplay between unknown genetic and environmental factors.

⁵ Breast cancer is another example. The two dominant loci, BRCA1 and BRCA2, for this syndrome account for about 3% of all cases. One must be wary, however, of overgeneralization of this principle.

violated. In short, testing some people within a pedigree could violate issues of doctor-patient confidentiality of other people in the pedigree.

A third lesson of AD concerns the importance of finding a gene. You may quite rightly question the importance of isolating these three genes when they account for less than 1 in twenty Alzheimer's cases. The major importance may actually be in the ability to learn more about the neurobiology and the disease process (AKA *pathophysiology*) of AD than in shouting to the world "Researcher Finds AD Gene." It is helpful to digress here for a moment to see how the gene discoveries have assisted in the understanding of AD. Again, the details are unimportant—it is the logic of the scientific quest that requires careful attention.

The locus for amyloid precursor protein (APP) on chromosome 21 codes for a polypeptide⁶ that eventually gets cleaved into certain sections. One of the longer fragments⁷ is chemically "sticky," so these fragments bind together (i.e., form *multimers*) and join with other chemicals. The long fragments were found to be heavily concentrated in the plaques and tangles of AD brains. Several of the mutations in the APP locus result in an increased proportion of the longer fragment. Also the effects of the two presenilin genes appeared to be associated with increased production of amyloid, especially the longer fragment. These findings (along with many others not reviewed here) have

The search for genes is in the early stages, so more Mendelizing forms for AD may be uncovered in the future.

⁶ The APP locus is actually more complicated than this simple statement implies. There are 19 exons in this gene and different mRNA sequences are made by gene splicing—linking together different exons in the editing process. For example, the most frequent APP polypeptide in brain (APP695) results from the splicing of exons 1 to 6, 9 to 13, and the last 5 exons while APP751, the most prevalent form elsewhere, inserts exon 7 into this sequence.

coalesced into the “amyloid cascade hypothesis” that holds that AD (or at least certain cases of AD) is due to some combination of amyloid overproduction and failure to appropriately break down and get rid of the longer beta-amyloid fragments.

This working hypothesis has guided research in many different directions, three of which will be mentioned here. The first is in the area of therapeutics. Scientists are now exploring ways to interfere in the normal process of amyloid degradation so that the longer, “sticky” fragment can get broken down more easily and are also investigating ways to digest the amyloid deposits in the plaques. A second area of research is into the genetics and the enzymology of those enzymes (called *proteases*) that cleave APP. Finally, researchers have placed a mutant human APP allele and mutant presenilin alleles into mice and found that these transgenic mice strains show similar plaques and tangles as AD. This is an especially exciting development because an animal model permits research and drug testing that cannot be done with humans.

At the same time, work on basic neurobiology is guiding genetic research. The neurofibres that become tangled in AD may be viewed as flexible railroad tracks that are prevented from tangling because they are spiked into a series of railroad ties. In the neuron, the chemical equivalents of the railroad ties are tau proteins, so the genes for tau proteins are being screened to see if mutations here may play a role in AD.

⁷ A-beta 1-42.

Genetics of AD: The Apolipoprotein E Locus

The 3 dominant genes for FAD account for a small fraction of cases. What is responsible for all the other cases of AD—that half of FAD that is not due to the 3 loci and all of sporadic Alzheimer's? It turns out that there is another gene, the APOE locus (for *apolipoprotein E*) that contributes to AD, especially the late onset form but it is expressed in a different fashion than the 3 loci. The three dominant loci appear to be fully penetrant—if a person has the deleterious allele at any one of these three loci, then the probability of developing AD is close to 1.0. In contrast, the APOE locus is viewed as a *susceptibility locus*—i.e., it increases the *likelihood* of developing AD but in no way guarantees that AD will occur.

The APOE locus codes for a protein that assists in the transportation of cholesterol throughout the body. It has long been of great interest to cardiology because of its role in heart disease, but the discovery of its association with AD was largely fortuitous. There are three alleles at the locus that are formally designated as $\epsilon 2$ (i.e., epsilon 2), $\epsilon 3$, and $\epsilon 4$ but will be called E2, E3, and E4 herein. E3 is the most frequent allele and E2 is the rarest, but the frequencies vary across populations. Among populations of European ancestry, the rounded-off frequencies are around .10 (E2), .15 (E4), and .75 (E3) [Gerdes, 1992 #127].

The E2 allele acts as a protective factor against AD while the E4 allele increases the risk for AD in a dose dependent way—i.e., the E4 homozygote is at higher risk than the E4 heterozygote [Farrer, 1997 #122; Rubinsztein, 1999 #26]. The E4 heterozygote

has about 2 to 3 times the risk and the E4 homozygote, around 10 times the risk, of developing Alzheimer's⁸, but actual risk figures vary according to ethnicity. The deleterious influence of E4 appears to be more pronounced in some Asian and white populations than in African-Americans [Farrer, 1997 #122; Tang, 1996 #124]. The E4 allele may also be associated with an earlier onset and more rapid course of illness. However, not everybody with the E4 allele develops AD, and many people without an E4 allele also develop AD. This is the reason why the APOE locus is referred to as a susceptibility or risk factor gene.

Testing for APOE is useful in research settings and in some clinical settings where a diagnosis of AD is already suspected. But should there be general population screening for APOE? This is still quite a controversial issue. Unlike many medical tests, knowledge of the APOE genotype in an otherwise healthy person is neither diagnostic nor prognostic. All statements about APOE are probabilistic, so the most a clinician could tell a person about his/her risk for AD is something akin to "maybe or maybe not." Enthusiasm for general testing is also dampened by the fact that there are no known ways to prevent AD. If an effective but costly prevention were developed, then it would make sense to genotype healthy individuals and devote scarce resources to those at highest risk of developing AD. A further issue muddling the debate is confidentiality. If accepted medical practice were to screen, then insurance carriers could know the results with untoward consequences for those at risk for AD. Hence, although there are no laws

⁸ The risk figures have been developed mostly from case-control types of studies in which allele frequencies are calculated from a group of patients with AD and community controls. The results of the

preventing a person from getting genotyped, most public policy statements by medical groups and patient-advocacy associations do not recommend screening at the present time. However, the same public policy statements recognize that screening may eventually be useful as science progresses and issues of confidentiality and insurability are resolved.

To summarize, there are four genes known to be involved in AD. Together, however, they account for only a small percentage of AD cases. The etiology of the majority of cases is obscure, so the models for these are more on the theoretical than empirical level. Hence, we embark into the great unknown to discuss phenocopies, polygenic transmission, and the multifactorial threshold model.

The Great Unknown: Phenocopies

Technically defined, a *phenocopy* is an environmentally produced phenotype that resembles a genetic syndrome. For classic Mendelian disorders, several intrauterine effects can produce a neonate with physical features resembling a known Mendelian disorder. For example, an autosomal dominant mutation can lead to Holt-Oram syndrome, which results in incomplete and deformed limb development. The drug thalidomide, if taken during a sensitive period of pregnancy, will produce similar malformations.

In a certain sense, the term phenocopy is chauvinistic. One could just as well invent the word genocopy to denote a genetic abnormality that results in the same

phenotype as a well-described environmental syndrome. Holt-Oram syndrome might be regarded as a genocopy of thalidomide toxicity. The terminology becomes even more confusing when the concept of a phenocopy is applied to a DCG. Ingestion of large amounts of lead and other heavy metals during infancy and childhood will lead to mental retardation in an otherwise normal person. Calling this a “phenocopy” carries with it a tacit assumption that mental retardation is a genetic syndrome.

To avoid a useless, hair-splitting discussion about terminology, the following is suggested⁹. The definition of a phenocopy given above is the one encountered in all textbooks on human and medical genetics. In practice, however, most researchers who work with DCGs that involve behavioral phenotypes (learning disabilities, psychopathology) use the term in a much looser sense. Here, a phenocopy refers to a person who may have any type of genetic vulnerability towards the disorder but in whom the etiology is clearly traced to a significant environmental event (or events) of very large effect. According to this definition, a psychosis resulting from prolonged amphetamine abuse may be regarded as a phenocopy of schizophrenia or brief reactive psychosis without any implication that either of the disorders are 100% genetic syndromes. It is this loose definition that will be used herein.

In terms of Alzheimer’s disease, there are no firmly documented phenocopies. However, there are several types of environmental factors that are being researched as

⁹ If the author really had his druthers, he would ban the term phenocopy entirely from DCG. Every example of a phenocopy could be included in multifactorial transmission, a model that will soon be described. Unfortunately, the term is in constant use in the professional field and hence cannot be avoided.

potential candidates. These include severe head trauma, stroke, and other forms of brain damage.

The Great Unknown: Oligogenic, Polygenic, and Who-Cares-A-Genic

Transmission

Many traits are the result of the combined effects of several different gene products (peptides, proteins, and/or enzymes) where each product is the result of the DNA blueprint at a different locus. When the effects of several different genes add and/or interact together to produce a phenotype, then the mode of transmission is called *oligogenic* (when the number of genes is on the small side) or *polygenic* (when the number of genes is large). There is not an exact number that separates oligogenic from polygenic transmission except for a rough order of magnitude—six genes is clearly oligogenic while sixty genes is obviously polygenic, but sixteen genes could be either oligo- or polygenic. There should really be no debate about the extent to which DCG are oligogenic or polygenic. At present, we lack the technology to determine the number loci that contribute to, say schizophrenia or major depression. Speculation as to that number is more akin to medieval scholastic arguments about angels and pinheads than contemporary science. In the remainder of this text, the word “polygenic” will be used to avoid the awkward phrase “oligogenic or polygenic” with the tacit implication that the number of genes involved need not be large.

It is helpful to give a hypothetical illustration of polygenic inheritance. Consider a continuous phenotype such as height and assume that three different genes contribute to

individual differences in height. Denote the three loci as the A, B, and C locus and let there be two alleles, denoted by an upper case and lower case letter, at each locus. At the A locus, assume that allele *A* adds 1.9 cm to height while allele *a* subtracts 1.9 cm from height¹⁰. Hence, genotype *AA*, having two *A* alleles will add 3.8 cm to height; genotype *Aa* adds 0 cm to height; and genotype *aa* adds -3.8 cm to height. Assume that allele B adds .6 cm to height and *b* subtracts .6 cm, and allele C adds .3 cm while *c* subtracts .3 cm.

The genotypes in the population will contain all combinations of the alleles at these loci—e.g. *AABbCc*, *AaBBcc*, etc. There will be 27 different genotypes. Assume that the influence of each locus adds together. Then the individual differences in height resulting from these three loci are given in Table X.X. To find the predicted height of a person, take the average height in the population and then add the amount in Table X.X corresponding to the person's genotype. For example, if mean height were 176.2 cm, then a person with genotype *AABbCC* would be predicted to be $176.2 + 4.4 = 180.6$ cm tall.

[Insert Table 6.1 about here]

Now it is time to learn some terminology from this example. Note that the three loci do not have equal effects. The ultimate influence of locus A on height is greatest and the influence of locus C is least. This would be called a *weighted polygenic system*. The alternative, an unweighted polygenic system, assumes that each locus contributes the

¹⁰ This is purely a mathematical convenience that should be translated as "all things being equal, individuals with one *a* allele are .8 cm shorter than people without an *a* allele." It does not imply that allele *a* physically shrinks a person.

same amount to the phenotype; the unweighted model is important for theoretical genetics but is implausible in nature¹¹.

In the weighted system, locus A would be called a *major gene* or *major locus* in the sense that it has a large influence on the phenotype. It would appear natural to refer to locus B and locus C as minor loci, but in the twisted logic of scientific language, the terms *modifying genes*, *modifying loci*, or even *background genes* are preferred. These are loci that have a relatively small quantitative effect on the phenotype.

Note how the effects of the alleles and the loci added together. For example, consider genotype *AABbcc*. There are two *A* alleles, each contributing +1.9 cm, one *B* allele (adding .6 cm) and one *b* allele (subtracting .6 cm), and two *c* alleles, each of which subtract .3 cm. Hence, the deviation for this genotype is $2*1.9 + (.6 - .6) + 2*(-.3) = +3.2$ cm. Hence, this is called an *additive model*. Once again, the additive model is an *assumption* and not a necessary consequence of nature. Departures from the strictly additive model occur when there is any degree of dominance or *epistasis* (i.e., statistical interaction among several genes) and will be discussed in a later chapter.

Finally, recall the phrase *predicted height* when we calculated the expected height of someone with the genotype *AABbCC* as 108.6 cm. An actual person with this genotype may not be exactly 108.6 cm tall because various environmental factors could influence the phenotype. It is often assumed that several different environmental

¹¹ The critical mathematical issue is not the weighted versus unweighted model but the differences in the weights. When the differences among the weights are on the small side, then the mathematics of an unweighted polygenic model give a very close approximation to the real state. At present, we do not have

factors¹² may contribute to the phenotype. When there are several genes and several different environmental factors contributing to a trait, then the model is usually referred to as *multifactorial*. The phrase *polygenic* is also used instead of multifactorial with the tacit assumption that environment may play a role in addition to genes.

The Great Unknown: The Multifactorial Threshold Model

The multifactorial threshold model applies polygenic transmission and several etiological environmental factors to a *discrete* or *dichotomous* phenotype. A discrete or dichotomous phenotype is one that can be classified into two or more groups with no intermediate phenotypes between the groups. Pregnancy is a classic discrete phenotype—women are either pregnant or not pregnant and it is impossible to be in between. Note that a discrete phenotype may still have sub-phenotypes that are graded continuums. For example, length of pregnancy is an important continuous variable with the category of pregnant women.

Polydactyly (i.e., having an extra toe on a foot) in mice is a classic example of the multifactorial threshold model. Ordinarily mice have four digits on a paw, but under some circumstances, a fifth digit may appear. The extra digit may be poorly formed and nonfunctional, but in terms of phenotypic classification, it is an all or none trait. Both genes and environment (especially prenatal stress) contribute to this phenomenon, but there is more than a single locus involved in the trait.

any empirical evidence as what the distribution of weights might be for behavioral phenotypes; the distribution may well depend upon the specific phenotype.

¹² Thankfully, the terms oligoenvironmentic versus polyenvironmentic are not found in the literature.

Originally developed by Falconer (19XX), the multifactorial threshold model was first applied to human behavior by Gottesman and Shields (19XX) in their classic twin study of schizophrenia. It has since become a very popular model of the transmission of psychiatric disorders and psychopathology and a version of it is depicted in Figure 6.1. The key concept of this model is *liability* (aka *susceptibility*, *vulnerability*, *predisposition*). Liability is not the disorder per se. Instead, liability is defined as an *unmeasured (i.e., latent) continuous variable that probabilistically relates to the disorder*. The higher one is in liability, the greater the chances of developing the disorder.

[Insert Figure 6.1 about here]

Genes contribute to the *genetic liability*. For example, genotype *AABbccDd* might contribute +1.3 units to genetic liability while genotype *aabbCcdd* might contribute -2.3 units to genetic liability. Because genetic liability is unmeasured, any “units” are completely arbitrary. It is customary, however, to let 0 denote the mean liability, and let positive numbers denote risk (i.e., a greater propensity to develop the disorder) and negative numbers denote protection (a lower probability of developing the problem).

Environmental factors contribute to *environmental liability* which has an analogous interpretation and measurement scale as the genetic liability but applies to environments instead of genes. Together, genetic and environmental liability contributes to *total liability*. It is the total liability that relates directly to the disorder. Once the total liability reaches a certain point (the *threshold*), then the phenotype changes and a disorder results. Note how only the total liability correlates perfectly with the phenotype. Knowing a

person's genetic liability permits *probabilistic* statements of the form, "Joe is at high risk for bipolar disorder" or "Susie is at reduced risk for agoraphobia," but does not allow one to predict with certainty that Joe will become bipolar and that Susie will never develop agoraphobia. Similarly, knowing a person's environmental liability permits only probabilistic statements about the development of a disorder.

The threshold model is developed in more detail in a later chapter. Here we note that the important fact is that the model is once again *a set of assumptions about how nature works*. It is not the case that all the genetic and environmental factors for a number of disorders have been clearly elucidated and the multifactorial threshold model emerged as a parsimonious mathematical explanation for the empirical data.

Overall Perspective of DCG

If we join the empirical evidence about the genetics of AD along with the speculations about polygenic transmission and the multifactorial threshold model, we arrive at the overall model proposed by Gottesman (1991) about the mode of genetic transmission for schizophrenia. Figure 6.2 presents an adaptation of this model but will be discussed here in terms of AD.

[Insert Figure 6.2 about here]

The figure partitions the etiology of AD according to its major (but not necessarily exclusive) causes. There are three Mendelian forms of the disorder, corresponding to the APP, presenilin 1, and presenilin 2 mutations. Although these three

forms have high penetrance, they account for only a small percent (4% in the cases of Figure 6.2) of all AD.

There are two major loci that contribute to AD. The first might be the APOE locus that is responsible for 8% of cases. This figure means that in 8% of AD, the APOE locus is the major cause for the disorder even though there may be many other genes and environmental factors that also contribute to the onset among this 8%. Note well that the 8% figure is completely hypothetical—we do not know how many AD cases have APOE as their major cause. In the future a second major locus may be uncovered that also contributes to susceptibility. This eventuality is portrayed in Figure X.2 as major locus 2 that is the major cause for 15% of cases.

The majority of cases—62% in Figure 6.2—may be due to the effects of many different loci and a variety of environmental factors that combine together and influence risk. This is the multifactorial threshold model that was discussed earlier and is denoted as simply “Multifactorial” in the figure. Once again, the estimate of 62% is fictitious. Most contemporary geneticists suspect that the multifactorial transmission will eventually account for the bulk of any DCG, but no one really knows that for certain.

Lastly, phenocopies account for the remaining 11%. Gross insults to the brain through trauma, viral infections, or a number of yet-unknown environmental factors might produce AD in people who are otherwise at low risk for AD. Again, the percentage here is complete, uneducated guesswork.

Taken together, this model implies that there is no single “cause” of AD. Rather, there are a number of different events, some large and some small, that lead to the same process or very similar processes. Just as many roads lead to Rome, there are different pathways to AD and the road traveled by one person may be very different from that taken by another. Some roads are superhighways (e.g., the three Mendelizing forms) that get one there in a hurry, but the majority are minor streets with twists, turns, detours, and dead ends. But everyone who enters Rome develops AD. As a result, the causative factors in one person could be quite distinct from the etiological events in someone else.

This overall model has long been applied to complex behavioral phenotypes such as mental retardation, specific learning disabilities, and every form of psychopathology. In every case, however, empirical knowledge about the relative contributions of Mendelizing forms, major loci, multifactorial transmission, and phenocopies is very rudimentary. For mental retardation, there are indeed many documented Mendelizing forms—PKU and Fragile X syndrome are but two of over one hundred—and several recognized phenocopies such as severe lead toxicity. And the ALDH-2 polymorphism illustrates the role of a major locus, at least in some Asian populations. However, slicing the rest of the pie is primarily guesswork. To complicate matters, the division of the pie for one DCG may be quite different from that of another disorder.

The Final Lesson for DCG: Genetics is a Tool, Not a Goal

The progress being made in AD research should reinforce a major lesson from our study of Mendelian traits. Finding a gene or genes for any disorder or behavior is not the

goal or holy grail of science. Instead, it must be looked upon as reaching a milestone in a long journey, the majority of which is still in front of us. All of us have had the experience of being on a long road trip and spending hours passing cornfield after cornfield, desert and desert, or town after town. When we arrive at a salient point—whether it be the halfway mark, an important geographical landmark, or a major city—our lethargy gives way to a momentary sense of excitement and renewal. But do we stop and consider the journey complete? Of course not! We trudge on until we arrive at the intended destination.

So it is with finding a gene for a disorder like AD or any other human behavior. It is an important accomplishment. It should be celebrated, and kudos should be bestowed on the discoverers. But finding a gene for schizophrenia, intelligence, extraversion is not the *raison d'être* of genetics. It is an important step in the long journey towards unraveling the biology behind a phenotype.

The importance of the Alzheimer's story is the interplay between the genetics and basic neurosciences. Genetics has lead to the development of transgenic animal strains that are exceptionally important for basic neuroscience research. In turn, the results of neurobiology will aid in the search for other genes that may influence the disorder. In short, for DCG, genetics is a tool, not an end in itself.

Table 6.1. Hypothetical effects of genotypes on height. The column labeled Amount gives the extent to which the genotype deviates from the population mean.

Genotype	Amount	Genotype	Amount	Genotype	Amount
<i>AABBCC</i>	+5.6	<i>AaBBCC</i>	+1.8	<i>aaBBCC</i>	-2.0
<i>AABBcC</i>	+5.0	<i>AaBBcC</i>	+1.2	<i>aaBBcC</i>	-2.6
<i>AABBcc</i>	+4.4	<i>AaBBcc</i>	+0.6	<i>aaBBcc</i>	-3.2
<i>AABbCC</i>	+4.4	<i>AaBbCC</i>	+0.6	<i>aaBbCC</i>	-3.2
<i>AABbCc</i>	+3.8	<i>AaBbCc</i>	+0.0	<i>aaBbCc</i>	-3.8
<i>AABbcc</i>	+3.2	<i>AaBbcc</i>	-0.6	<i>aaBbcc</i>	-4.4
<i>AAbbCC</i>	+3.2	<i>AabbCC</i>	-0.6	<i>aabbCC</i>	-4.4
<i>AAbbCc</i>	+2.6	<i>AabbCc</i>	-1.2	<i>aabbCc</i>	-5.0
<i>AAbbcc</i>	+2.0	<i>Aabbcc</i>	-1.8	<i>aabbcc</i>	-5.6

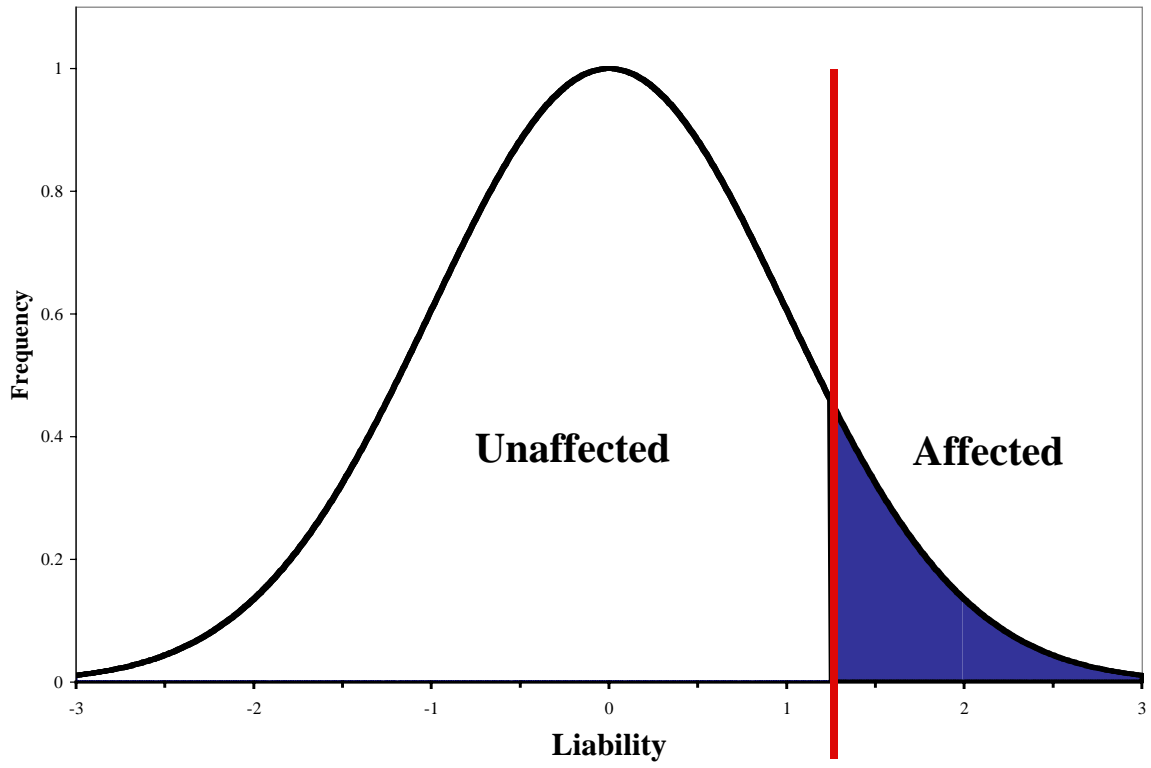


Figure 6.1. The multifactorial threshold model.

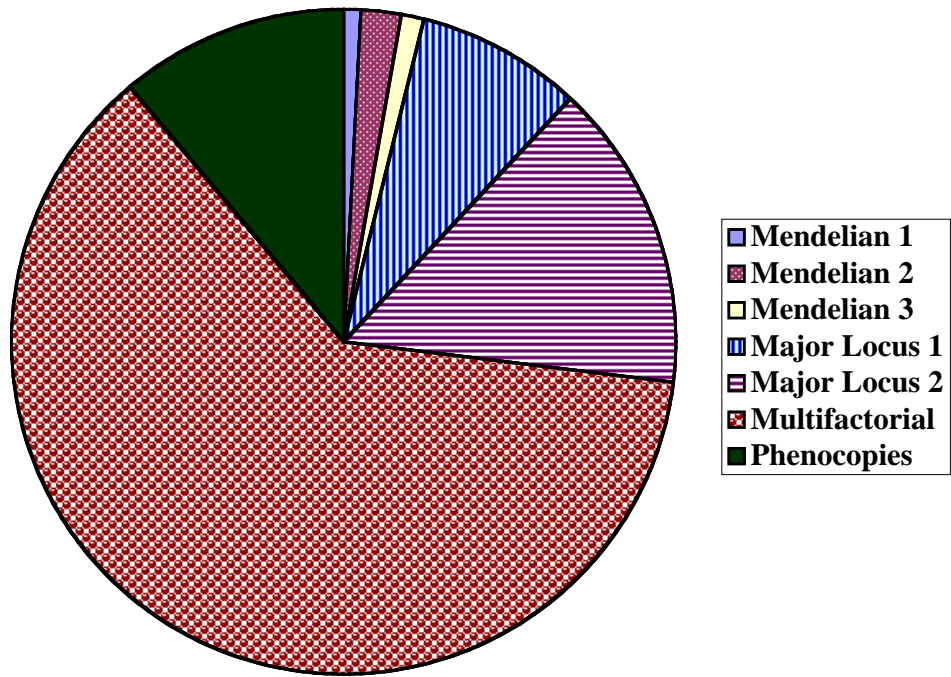


Figure 6.2. Principal etiological causes of a DCG.