Genetic Predisposition: Is the Human Organism Predisposed to Addictive Disorders?¹

**ARTICLE**

**Introduction**

Few would argue that substance use and its related problems is a global social health concern. Likewise, most knowledgeable people agree that a multitude of environmental factors such as culture and family structure influence drug-taking behavior, for example, at what age a person will begin using psychoactive substances. However, there is less agreement regarding genetic predisposition as a primary determinant for addictive disorders. Is it more likely that a person’s susceptibility to becoming biomedically dependent upon a psychoactive substance is determined by one’s genes than one’s culture or upbringing? This paper will attempt to present some of the scientific research completed over the past century and give evidence of and credence to the theory that alcoholism and drug addiction are inherited disorders. That the genetic components that influence susceptibility are in fact apparent and it is nature, not nurture that determines one’s likelihood of becoming chemically dependent once the use of a psychoactive substance begins, and therefore, it is a person’s genetically inherited biology that predisposes a person to psychoactive substance use disorders.

**Review of Literature**

Defining genetic predisposition: Predisposition (pre-dis-po-si-tion) is defined as a latent susceptibility to disease that may be activated under certain conditions. A genetic predisposition is a genetic effect which influences the dominant and recessive phenotype of an organism but which can be modified by the environmental conditions. The phenotype of an individual organism is either its total physical appearance and constitution or a specific manifestation of a trait, such as body size, eye color, or behavior that varies between individuals. Phenotype is determined by and large by genotype, or by the identity of the alleles that an individual carries at one or more positions on the chromosomes. “DNA is packaged into compact units called chromosomes” (Sheppard, 2005). An allele gene is a paired gene whose genetic difference from a normal gene may be responsible for the more than 3,500 chromosomally linked human diseases (Inaba and Cohen, 2000). Normally, the alleles have the same function, e.g., two alleles control eye color but one is for blue eyes and the other for brown eyes. One explanation for why some humans are more susceptible to substance dependence disorders may be found in allele genes. “In terms of addiction, one allele may be responsible for normal alcohol metabolism while the other does the same job but does it poorly so the alcohol has a greater effect” (Inaba & Cohen, 2000).

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However, many phenotypes are determined by multiple genes and are influenced by various environmental factors. Thus, the identity of one or a few known alleles does not always enable prediction of the phenotype.

Nevertheless, because phenotypes are much easier to observe than genotypes (it doesn't take a degree in chemistry or genetic sequencing to determine a person's eye or hair color), classical genetics uses phenotypes to deduce the functions of genes. By using breeding experiments, early genetics pioneers could check these inferences and were able to trace inheritance patterns with limited knowledge of molecular biology and make assumptions about the transference of various characteristics and traits that were passed from parent organisms to offspring. Today, laboratory testing enables scientists to identify individuals who are genetically predisposed to certain health problems such as diabetes, alcoholism or even substance abuse.

The History of Genetics

Mendelian Genetics. Mendelian inheritance or Mendelian genetics is a set of primary tenets relating to the transmission of hereditary characteristics from parent organisms to their children. They were initially derived from the work of Gregor Mendel published in 1865 and 1866, which was "re-discovered" in 1900, and were initially very controversial. When they were integrated with the chromosome theory of inheritance, a theory proposed by Thomas Hunt Morgan in 1915, they became the core of classical genetics.

Gregor Mendel was an Austrian monk who conducted plant hybridity experiments in the 19th century. Mendel derived the laws of inheritance and is known today as the “father of genetics”. Between 1856 and 1863, Mendel cultivated and tested some 28,000 garden pea plants. His experiments gave birth to two generalizations that later became known as Mendel’s Laws of Heredity or Mendelian Inheritance. These are described in his paper "Experiments on Plant Hybridization" that was read to the Natural History Society of Brno, Moravia on February 8 and March 8, 1865, and was published in 1866. Mendel’s research focused primarily on the mechanisms of heredity and evolution. His experiments allowed him demonstrate scientifically that genes have dominant and recessive characteristics and that these characteristics are passed from one generation to the other most unerringly as the species produces offspring, thus essentially opening the door for further scientific study of human genes and what is now known as the Genome Project.

The Drosophila genome

*Drosophila melanogaster*, the a common fruit fly, is a little insect about 3mm long, of the kind that accumulates around spoiled fruit. It is also one of the most valuable organisms used in biological research, particularly in genetics and developmental biology, and has been used as a model organism for research for almost a century. Today, several thousand scientists are working on many different aspects of the fruit fly. Its importance for human health research was recognized by the award of the Nobel Prize in medicine and physiology to Ed Lewis, Christiane Nusslein-Volhard and Eric Wieschaus in 1995. Part of the reason researchers work with Drosophila is historical - so much is already known about it that it is well-understood - and part of it is practical: it’s a small animal, with a short life cycle of just two weeks, and is cheap and easy to keep large numbers. Mutant flies,
with defects in any of several thousand genes are available, and the entire genome has recently been sequenced.

Thomas Hunt Morgan, a renowned late 19th century geneticist and 1933 laureate of the Nobel Prize in physiology and medicine, is best known for his work with Drosophila. Morgan’s discoveries formed the basis for modern genetics research and present day theories pertaining to how organisms obtain their hereditary materials. Using the fruit fly, Morgan was able to demonstrate that genes are carried on chromosomes and are the mechanical basis of heredity. Life cycle of Drosophila: why this common fruit fly is ideal for research.

The drosophila egg is about half a millimeter long. It takes about one day after fertilization for the embryo to develop and hatch into a worm-like larva. The larva eats and grows continuously, molting one day, two days, and four days after hatching (first, second and third instars). After two days as a third instar larva, it molts one more time to form an immobile pupa. Over the next four days, the body is completely remodeled to give the adult winged form, which then hatches from the pupa casing and is fertile within about 12 hours. (The timing is for 25°C; at 18°C, development takes twice as long.)

The Drosophila has four pairs of chromosomes: the X/Y sex chromosomes and the autosomes 2, 3, and 4. The fourth chromosome is quite tiny and rarely heard from. The size of the Drosophila genome is about 165 million bases and contains an estimated 14,000 genes (by comparison, the human genome has 3,400 million bases and may have about 22,500 genes; yeast has about 5800 genes in 13.5 million base bases).

**Empirical research**

In the mid-1970’s, Donald W. Goodwin, a prominent physician and educator at Washington University School of Medicine became interested in alcoholism and was well aware of the difficulty in separating the effects of heredity and the effects of environment. Goodwin, best known for his work with identical twins, observed: “Many things run in families: diabetes, speaking French, musical talent, voting Republican, money, longevity, and so on. But this does not mean that these things are genetic.” (Goodwin, 1976, p. 53) In his first major publication “Is Alcoholism Hereditary?” Goodwin observed:

The notion that alcoholism is hereditary is old, older than theories that alcoholism comes from environmental factors such as early weaning or growing up in slums. For most eighteenth- and nineteenth century physicians, chronic drunkenness, or alcoholism, sprang from a “constitutional weakness” passed on from generation to generation. The fact that alcoholism was a “family disease” probably was better appreciated by our Victorian ancestors than by the present generation. For our great-grandmothers, alcoholism was a vice, but the sinner was not entirely a voluntary sinner. “Of course, his father was that way, and his mother’s father drank too,” was a stock Victorian observation, implying that heredity was the link. (p. 43) 4

Goodwin (1976) also noted that, “To know whether a disorder occurs more often in some families than in others, it is necessary to know how often the disorder occurs in the general population” (p. 43). In other words, the sample being studied must be representative of the population in order for findings to be scientifically meaningful. Since Goodwin, many epidemiological studies have been conducted to determine the prevalence of alcoholism in the US, as well as in other countries. In fact, studies in the United States as well as many other

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countries have consistently reported higher rates of alcoholism in the families of alcoholics than in the general population. Goodwin, referring to his own research as well as a host of early studies conducted by such renowned alcoholism researchers as E.M. Jellinek (1890-1963) founder for the Center for Alcohol Studies, Erik Stromgren of Germany (Genetic Implications of Alcoholism) and others who compared families of alcoholics with families of non-alcoholics found that, while studies varied in their statistical significance, they almost always reflected a higher prevalence of alcoholism among individuals who were products of at least one alcoholic parent. Goodwin noted, “The evidence for multiple causes of alcoholism is no better or worse than the evidence for a single cause. The cause of alcoholism in truth, is unknown. But it does run in families, and this is a starting point.” (Goodwin, 1976, p. 48-49).

Enter the famous twin studies undertaken in Sweden, Finland and the United States in an attempt to associate alcoholism to genetic causation. The Swedish study involved 174 sets of male twins. The concordance rate for identical twins was 54%, meaning alcoholism rates for identical twins was far greater than that of fraternal twins which was 28% (Goodwin, 1976, p. 80). In the Finish study, 902 male twins, both identical and fraternal, were used. Interestingly Goodwin (1976) noted, “In contrast to the Swedish study, no difference was found between identical and fraternal twins with regard to the consequences of drinking . . .” However, “More or less normal patterns of drinking . . . did appear to reflect genetic factors.” And with regard to frequency and amount of drinking there was “significantly more concordant among identical twins than among fraternal twins” (Goodwin, 1976, p. 81).

In the twin study conducted in the United States in which n=850 pairs of like-sex twins investigators found that identical twins were more concordant for “heavy drinking” than fraternal twins. (Goodwin, 1976, Cloninger & Bohman, 1986) showed that a male child of just one alcoholic parent had a 34% higher risk for becoming alcoholic than those of the non-alcoholic parent, suggesting that, while environment plays an important role in shaping behavior, there is also a genetic link that may reveal itself as more powerful and influential in determining a person’s susceptibility to alcoholism or substance dependence disorders than has been previously thought. These genetic influences in effect, predispose a person to addictive disorder.

**Environmental Influence**

Environmental factors fundamental to families and communities that can influence behavior in a positive or negative way are many and varied. They can include environmental and work-related stress, violence and abuse, family relationships, health and nutrition, to name just a few. Environmental influences have their greatest impact on the developing brain in the first 10 years of life (Inaba & Cohen, 2000, p.65). However, these factors, while they do have some influence on behavior, are much more subjective and it is much more difficult to attribute alcoholism or addiction solely to the lack of nutrition or domestic violence. It is more probable that a combination of environmental factors contributes to a person’s drug taking behavior. However, we are left with the questions as to why one individual who grows up in an abusive family becomes alcoholic or chemically dependent while another who grows up in a similar situation with a similar parenting style does not. Scientific research may be able to unravel the mystery. Biochemical research suggests that, once having been genetically predisposed to substance use disorder, environmental “risk factors” increases a person’s likelihood of becoming addicted to a substance once drug-taking begins.

In order to better understand the role of genetics in the biology of addiction we need a closer examination of classical genetics research. In 2001 the genome of the Drosophila was completely sequenced and analysis of the data is now mostly complete. Several other insect genomes have now been sequenced, including many Drosophila species, the genomes of
mosquito and honeybee, and these are starting to show what is common among all insects, and what distinguishes them from each other.

**Genetic variation**

Genetic variation refers to the variation in the genetic material of a population or species, and includes the nuclear, mitochondrial, ribosomal genomes as well as the genomes of other organelles. New genetic variation is caused by genetic mutation, a theory proposed by Hugo De Vries in 1900, which may take the form of recombination, migration and/or alterations in the *karyotype* (the number, shape, size and internal arrangement of the chromosomes). *Genetic drift* is a statistical measure of the rate of genetic variation in a population (Kandel, 1999).

All humans are members of the species, Homo sapiens, but no two humans are exactly alike. Even for twins, there are slight differences in their DNA. There are many similarities and differences among people in the global population. For example, eye color and blood type differ among individual Homo sapiens. Differences in these traits are due to genetic differences, or genetic variation. The human gene pool carries alternative alleles that affect blood type and many other traits. Other species also have variation in their gene pools. For example, apple trees are all members of one species, but the fruit produced by different trees can be red or yellow, hard or soft, sweet or tart, large or small. These differences are caused partly by genetic variation. When two or more alleles of a gene are present in a gene pool, the population is said to be polymorphic.

The interaction between genotype and phenotype has often been conceptualized by the following relationship:

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genotype + environment = phenotype
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A slightly more nuanced version of the relationships is:

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genotype + environment + random-variation = phenotype
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Illustrating genetic variance in phenotypes, individuals in the mollusk species demonstrate diverse coloration and patterning.

A phenotype is any detectable structural, biochemical, physiological and behavioral characteristic of an organism and is determined by an interaction between its genotype and the environment. An example of the importance of random variation in phenotypic expression is the Drosophila in which its number of eyes may vary (randomly) between left and right sides in a single individual as much as they do between different genotypes overall, or between clones raised in different environments.

Dominant allele: Dominance relationship.

In genetics, dominant/recessive alleles derive one’s phenotype. A dominant allele refers to a genetic feature that “hides” or suppresses the recessive allele. A dominant allele causes a phenotype that is seen in a heterozygous genotype. Pairs of complementary genes determine many traits, each inherited from a single parent. Often when these are paired and compared,
one gene (the dominant) will be found to effectively shut out the instructions from the other, recessive gene. For example, if a person has one gene for blue eyes and one for brown, that person will always have brown eyes because brown eyes is the dominant trait. For a person to have blue eyes, both their genes must be blue (recessive). When a person has two dominant alleles, they are referred to as **homozygous dominant**. If they have one dominant allele and one recessive allele, they are referred to as **heterozygous**.

A dominant allele when written in a genotype is always written before the recessive gene in a heterozygous pair. A heterozygous genotype is written Aa, not aA. Thus, Dominance/recessiveness refers to phenotype, not genotype.

Usually, this masking effect is a result of the loss of some function of the recessive gene that the dominant gene has retained. For example, in the case of ABO blood types, the O type is recessive because it does not produce any antigens or antibodies, whereas A and B types (which are co dominant) do. Or, in the above case dealing with eye color, there is a complete loss of pigment in blue-eyed people; therefore to express the phenotype, both copies of the gene (after all, humans are diploid) must have that same loss of function.

**Codominance and incomplete dominance**

Codominance means that it is neither dominant nor recessive. In certain cases, a "blend" of genes will occur because neither of the two genes of a genotype are dominant over the other. As an example, in blood cells, the trait for blood type has three different alleles: type A, type B, or type O, with O being recessive. If a father passes a gamete with the allele of type A and the mother passes on type B, then codominance results, with the offspring being type AB since neither allele type dominates the other.

Incomplete dominance occurs when a certain recessive gene appears within the phenotype of the organism, causing a blend between both the dominant and recessive gene.

Occurrence of dominant negative as described by William S. Klug, *Concepts of Genetics*: A dominant negative mutation occurs when the gene product adversely affects the normal, wild-type gene product within the same cell. This usually occurs if the product can still interact with the same elements as the wild-type product, but block some aspect of its function. Examples: A mutation is a transcription factor that removes the activation domain, but still contains the DNA binding domain. This product can then block the wild-type transcription factor from binding the DNA site leading to reduced levels of gene activation.

A protein that is functional as a dimer. A mutation that removes the functional domain, but retains the dimerization domain would cause a dominant negative phenotype, because some fraction of protein dimers would be missing one of the functional domains (Klug, Concepts of Genetics. Prentice Hall ).

This raises the question as to whether this type of genetic “mutation” might be responsible for an increased susceptibility to disease.

Population geneticists have studied the gene pools of many species of plants and animals. They have examined variation in obvious traits such as shape and color. In many cases, they have also found genetic variation in the amino-acid sequences of proteins and the nucleotide sequences of DNA. For example, the fruit fly, Drosophila melanogaster has an enzyme called alcohol dehydrogenase. (the principal enzyme in the human liver responsible for metabolizing alcohol). There are two slightly different forms of alcohol dehydrogenase that can be distinguished by electrophoresis, an analytical method frequently used in molecular biology and medicine for the separation and characterization of proteins, nucleic acids (DNA and RNA) and subcellular-sized particles like viruses and small organelles.

The two forms of alcohol dehydrogenase differ by only one amino acid. The amino acid difference is caused by one nucleotide difference in the DNA. Thus, in natural populations all
over the world, Drosophila melanogaster gene pools are polymorphic for the alcohol dehydrogenase gene. (This phenomenon is most likely due to the fact that the fruit fly takes its sustenance from spoiled or fermented fruit.) Populations of Drosophila have both types of alleles and produce both varieties of alcohol dehydrogenase. In one study researchers at Kossuth Lagos University in Hungary discovered that strains of the Drosophila fly differed in tolerance to alcohol and natural populations of the fruit fly exhibit genetic variations with regard to alcohol tolerance. Additional review of scientific research reveals that markers on four sets of chromosomes of mice have been associated with ethanol withdrawal severity (Crabbe, Buck, Metten, and Belknap 1990) and cocaine and amphetamine rapidly activates immediate early genes (IEG’s) indicating that drugs of abuse can profoundly influence the expression of genes (Grzanna & Brown, 1993).

Nature verses Nurture
Scientists have known for years that many human traits and the initial chemistry of the nervous system are passed on through generations by genes. More recently, researchers have attributed more complex physiologic reactions, human diseases and behaviors to a “genetic predisposition” for such characteristics (Inaba & Cohen 2000). Is it possible that humans have a genetic predisposition to addiction due to an alcohol dehydrogenase polymorphism or an amino acid variance? Researchers are hot on the trail to find the answers to these complex questions. What is DNA? In order to better understand genetic predisposition it is important to look more closely at the human body and what it is made of. The human body is made up of one fundamental unit, the cell. There are many different types of cells, each one made up of protein and fat. The nucleus of the cell is where DNA, an abbreviation for deoxyribonucleic acid, is located. DNA is made up of long chains of nucleotide molecules (nucleic acids). “Each organism has its own set of DNA including humans. . .” that makes it unique and different than any other organism. “An organism’s complete set of DNA is called its genome.” (Sheppard, 2005).

There are four major nucleotides that make up each “strand” of DNA: adenine, cytosine, guanine and thymine. Along these strands of nucleotides is where we find the genes. “Genes are essentially the blue print or step by step guide for the way our bodies are made. They contain all of the directions for building the proteins that our bodies require to function.” (Crabbe, et al)

A great plethora of literature documenting strain differences in response to virtually all drugs of abuse abounds. A major advantage of inbred strains is their genetic stability. “It is becoming widely accepted that most, if not all, drug responses are subject to influence by genetic factors . . . . Most drug responses are not simple genetic traits; rather, multiple genes can be demonstrated to influence a given response” (Crabbe, Buck, Metten & Belknap, 1990). In their research, Crabbe, et al discuss methods of tracing pathways from genes to drug-related behaviors and analyze drug response traits among “inbred” laboratory animals. Because inbred strains of mice differ markedly in their consumption of alcohol solutions (McClearn and Rodgers, 1959, cited in Crabbe et al) comparisons of multiple strains on multiple traits can be used to estimate genetic correlations. Using this approach, mice from 15 inbred strains were tested for severity of acute alcohol withdrawal following injections of 4 grams per kilogram (g/kg) ethanol. The same mice were tested 1 to 2 weeks later for severity of withdrawal from pentobarbital. There were significant differences in withdrawal from both drugs suggesting that about half of

6 Crabbe, J. C., Buck, J.K., Metten, P., and Belknap, J.K. Strategies for identifying genes underlying drug abuse susceptibility. Oregon Health Sciences University, Portland, OR.
the genetic variability in each of the strains response is shared and is presumed to be due to pleiotropic influence of some genes on both responses (Metten and Crabbe 1994). More significantly, studies with mice selectively bred to express withdrawal prone or withdrawal resistant ethanol withdrawal handling-induced convulsions have shown that they differ in severity of withdrawal from a variety of selected psychoactive substances, to include “several other alcohols, and acetaldehyde” (Belknap et al. 1987, 1988, 1989; Crabbe et al. 1991). Strain differences were statistically significant (genetically correlated) for all the drugs tested.

“Traditional analyses of drug sensitivity using genetic animal models such as those described above are able to estimate degree of genetic influence, and to identify response clusters of genetic codetermination” (Crabbe et al. 1990). For most drug responses, no specific gene has been identified in this research. “Traits affected by multiple genes usually display a continuous degree of response (rather than all-or-none responses), and the genes responsible are referred to as QTL’s” (Crabbe et al.) Collectively, they influence a “major portion of drug responsiveness.” QTL gene mapping depends upon linkage, or the tendency of genes physically close to one another, to be inherited as a unit. In contrast, unlinked genes tend to be inherited independently in accordance with the principles of segregation and independent assortment (Crabbe and Belknap 1992).

Discussion and implications

As we have seen from the genetic research presented here, the challenge of someday identifying a specific gene or set of alleles that is responsible for “turning on” predisposition to alcohol and drug addiction is a daunting one, particularly when one considers that the human genome contains an estimated 22,000 genes. While we are able to make inferences about genetic predisposition and susceptibility there are many questions that remain unanswered. “It would be useful to determine how many genes influent the trait, what their function is, and where they are located on the genome” (Crabbe et al. 1990).

In the past, the field of addiction relied on the study of biological twins to support the notion of a genetic link to addiction. (Tapert, Schweinsburg.) Today, modern technology now affords us the ability to map the human genome and look for the gene or genes (or allele) that may lead us to the genetic link addiction as well as other compulsive behaviors. This research, if it can be extrapolated to human behavior, is a clear indicator that addiction has a genetic component. Case control studies have shown evidence of multiple genes associated with addiction giving rise to the theory of polygenic inheritance.

“A major goal in drug abuse research is to determine the neurobiological mechanisms by which drugs of abuse produce tolerance, dependence, and addiction.” (Grzanna & Brown, 1993)

Another important objective should be to bridge the gap between science and treatment implementation.

Conclusion

In any case, increased understanding of the diathesis of addiction as the result of environmental AND genetic influences can help us in a variety of ways. A scientific knowledge of predisposition can aide healthcare and treatment providers by having the effect of the development of improved treatment for substance abuse problems and thereby improved treatment outcomes. More specifically, in-depth treatment planning that, while unable to do anything about a patient’s genes, may help the patient reduce and cope with daily stress, manage environmental risk factors and utilize community resources in ways that enhance and optimize patients’ success in treatment. An increased knowledge base and understanding of predisposition (factors both genetic and environmental that put a person at risk) should help us to identify potential problem drinkers and drug users early and prepare more effective prevention programs. It may also
assist legislators responsible for managing public funds in their decisions about public policy and the distribution of funds.

Continuing research will help to bridge the divide between science and the treatment community and shed light on the problem of substance use in the communities in which we live, challenge persistent perceptions of the drug addict as a “throw-away” citizen and hopefully reduce or even erase the stigma associated with addiction, so that those in recovery from substance dependence, and those who seek it may have equal opportunity to live happy productive lives.

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