

What Causes ADHD?

Russell A. Barkley, Ph.D.

One could write whole book chapters on the topic of etiologies of ADHD, as I did for my 2015 edition of my textbook, *ADHD Handbook for Diagnosis and Treatment* (New York: Guilford Press, Guilford.com). And entire books have been written on it, such as that more than a decade ago by Joel Nigg, Ph.D., in 2006 (*What Causes ADHD?* Guilford.com). There are 1,000+ studies published per year now on ADHD in the science journals. A substantial minority of these journal papers is on the causes of the disorder, so the field is moving rapidly to a greater understanding of causal mechanisms. I will briefly describe these causes here, but also address two related issues: Is ADHD a myth? Is it misdiagnosed or over-diagnosed?

Simply put, the etiology of ADHD is complex and can involve multiple causes. To date, all of the major ones fall in the realm of neurology and genetics (biological causation) with no evidence that social factors alone can account for the condition. However, there is some evidence that a few social factors (chronic stress, global adversity) might interact with genetic liability to the disorder to exacerbate it. But most such environmental factors that are related to ADHD are in the category of biohazards, such as head trauma, other neurological injuries, lead poisoning or other toxin exposures such as alcohol use during pregnancy, significant premature birth, etc. I will explain those further below.

Here is a relatively simple explanation of the complex causation of ADHD.

ADHD represents the extreme end of the distribution of several highly correlated normal traits in the human population, just like intelligence. In this case, these are inattention (specifically distractibility, poor persistence or sustained attention), inhibition, and executive functioning (self-regulation). When the degree of deficits (symptoms) in these traits reaches a certain point where they lead to

harm to the individual (impairment in major domains of life activities, increased risk for injury or death) then these deficits become a disorder. So the status of a "disorder" begins where harm or impairment begin in such cases of dimensional traits - in short, the environment kicks back creating adverse consequences for the individual at the extreme lower end of these trait dimensions (or higher end of symptoms).

What causes the variations in these traits in the human population, especially at the extremes? Far and away, the most significant contributor is genetics. Many studies show that variation in ADHD traits is largely determined by variation in human genes (about 55-90% of the variation, averaging to approximately 75-80%). This is just short of the genetic contribution to human height, is far greater than the genetic contribution to IQ or human personality traits, or is twice the contribution made by genetics to mental disorders like depression or anxiety, and is rivaled in its genetic contribution by just a few other psychiatric disorders like autism spectrum disorder and bipolar disorder. So the contribution of genetics to ADHD is substantial in explaining most of the variation among people in ADHD traits.

These genetic effects can occur in several ways. The first is by inheritance. The child inherits the genes for ADHD from their parents. Scientists have identified about 25-45 genes related to ADHD symptoms based on genome-wide scans. So the disorder is polygenic, meaning multiple genes contribute to the disorder with each likely contributing a small risk - but a combination of them creates increasing risk for disorder. The more risk genes you have the greater the risk for expressing the phenotype of the disorder. While we all may have these gene types, they are known to vary among people in the number of copies they receive (the length of the entire gene complex), known as tandem repeats, or polymorphisms. While all of us have the DRD4 or DAT1 gene, for instance, these genes occur in multiple copies sitting side-by-side (tandem repeats) along a chromosome. Most people may have 3-5 copies of the DRD4 gene. People with ADHD tend to have more copies of these genes, such as 7 or more repeats of this DRD4

gene. The number of copies of the gene alters the length of the protein it creates and that alters how it functions in the brain. In some cases, there is an extra copy of the gene inserted on the chromosome while in others there may be a section of the gene that has been deleted.

All of the genes we have identified to date for ADHD are expressed in the brain, not only in neurochemical expression such as dopamine and norepinephrine sensitivity and reuptake into nerve cells after release, but especially in how nerve cells migrate and then terminate in various brain regions, how they may be pruned later in development, or even how many synapses they form in connecting up to other nerve cells. Or the problem could be in the architecture of the cell. For instance, it might have too many reuptake transporters at the terminals or pre-synapse. These act like little vacuum pumps that absorb the neurotransmitter back into the nerve cell too quickly after it has been released into the gap between nerve cells (the synapse). Or perhaps it has too many alpha-2 ports along its axon or cell trunk that allow too much "noise" to degrade the nerve signal traveling along that axon. Or it may have a membrane at the post-synapse that is less sensitive to a neurotransmitter, such as dopamine. In that case, the typical amount of dopamine that gets released and attaches to the next nerve cell is not enough to "fire" or activate that next "insensitive" nerve cell. Or the gene could simply impact on how well the nerve cell is nurtured or functions thereafter.

Other evidence of inheritance for ADHD is that ADHD runs in families, so to speak, with relatives of children with ADHD being at greater risk for also having the disorder - the closer the relationship genetically to the child with ADHD, the greater the risk to the relative. So, 25-35% of parents of ADHD children are adults with ADHD, 25-50% of siblings of children with ADHD have ADHD, and 70-92% of identical twins of a child with ADHD have the disorder.

The second way genetics can affect expression of the disorder is through the occurrence of new (de novo) mutations in the genes of the child that are not present in the genome of the parents. We

think this may account for at least 10% of ADHD, especially if they are new cases arising in a family that has no increased risk among the relatives. New mutations can arise in the gametes (egg and sperm producing cells) simply from the length of time a person is alive, as we are exposed to mutation causing agents all the time, such as the sun's rays, X-ray machines, environmental toxins, etc. The longer we live, the more mutation-causing agents we are exposed to and so the more mutations we may accumulate in these gametes. These gene mutations are then passed on to that particular child even though they are not present in the DNA of the parent as might be found in their blood cells. Such de novo mutations are now known to contribute to about 25% of all new cases of autism spectrum disorder, for instance, and likely increase in risk of occurrence with the age of the parents, especially in fathers over 30 but also in mothers. We think the same thing is happening in ADHD as well.

A third way genes may contribute to ADHD is through gene-by-gene interaction. Thus, if you get one risk gene for ADHD, there is just a small or even trivial increase in terms of risk for disorder. But in the presence of a second or third ADHD risk gene, the effects of each gene are magnified in such a way that the risk is far higher than a mere additive effect of each gene added to the next, as I discussed above. Research on gene x gene interactions in ADHD is in its infancy.

A fourth way genetics can affect the occurrence of ADHD is by gene-by-environment interactions. A child inherits genes for ADHD that cause a susceptibility to the disorder and the expression of these genes then interacts with some other agent in the environment to magnify the risk for ADHD beyond the genes alone. For instance, maternal alcohol use (or tobacco) during pregnancy increases the risk for ADHD about 2.5 times the population risk. But should a child have one or two of the risk genes for ADHD, the occurrence may go up 8 times that of the population risk. Such agents can also be exposure to infections, chronic elevated parental stress during pregnancy, adverse early environments such as malnutrition or placement within a poor orphanage (as occurred in Romania during

its revolution), etc.

A fifth way genetic effects can influence ADHD occurrence is through "epigenetics." This is a term that refers to small chemical "flags" (usually methylated tags) that get inserted or attached on to a gene during or after its transmission to an offspring. The flag or tag affects whether or not that gene is activated, when it may get activated, and even what it may create to some extent if it is activated. There is evidence in other medical or psychiatric disorders, like autism, for such epigenetic effects. And some evidence is just beginning to accrue that it might occur in ADHD as well. In fact, it may be that the environmental effects discussed above (such as malnutrition in parent or child, chronic stress during pregnancy, or substantial social adversity) have their interactions with genes through influencing the extent to which such epigenetic tags are placed on genes.

A sixth way genetics can influence ADHD development is through major damage, duplications, or deletions to entire chromosomes, such as in genetic disorders like Down's syndrome, velocardial-cranial-facial (VCF) syndrome, Williams disease, and many other such major chromosome disorders. I have listed these genetic effects above in order of their likely contribution to ADHD, so this last one causes just a small percentage of cases because these are relatively rare events.

All in all, about 65-75% of all ADHD cases might be estimated to arise from these 6 genetic mechanisms, but chief among them is the inheritance of ADHD risk gene variants.

The remaining cases of ADHD are not genetic, but likely arise from neurologically compromising events: early brain injuries or maldevelopment alone (no genetic effects) when some event or agent damages the development of certain brain areas related to ADHD traits, such as the prefrontal cortex, basal ganglia, and cerebellum. Many of these risks occur during pregnancy, such as significant prematurity of delivery, significantly low birth weight, exposure to multiple infections, maternal alcohol use, maternal tobacco use [arguably], other toxins such as mercury, maternal

malnutrition, maternal medical disorders like diabetes, high levels of phenylalanine (causes PKU) in mother or baby or both, etc. These likely explain about 15-25% of ADHD cases in total.

Other biohazards occur after birth, such as head trauma, tumors, strokes, lead poisoning during the first few years of life, perhaps some dietary additives like food coloring (very small influence in a minority of children) or low levels of nutrients (like iron), etc. The latter causes after birth, combined, probably account for 5-10% or ADHD or less.

So all of this is to say that most of the causes of ADHD are genetic or neurological (or both). Yet certain events or agents in the environment can also cause ADHD or interact with ADHD risk genes to lead to its occurrence. Even so, we have no evidence that social factors by themselves, such as parenting, exposure to computers or video games, quality of education, peer influences, etc. contributes directly to the risk for ADHD.

The brain regions involved in ADHD are reasonably well understood now (about 5 or so). More recent work is advancing our understanding of brain microstructure (white matter) problems and problems with the functional connectivity of brain regions that are connected by such white matter fiber bundles.

As for ADHD being a myth, such ideas are perpetrated by those who either manifest a stunning ignorance of the science of ADHD (more than 25,000 scientific papers exist on it) or more likely are intentional efforts to mislead the public, such as by fringe political or religious groups (e.g., Scientology) or even professional competitors with their own therapies to market that rely exclusively on environmental theories of children's mental problems (psychoanalysts), and so have nothing to do with reflecting our true state of knowledge.

As for misdiagnoses (calling a child with another disorder as having ADHD instead or vice versa), there are undoubtedly instances of this in clinical practice. Not all clinicians are equally rigorous in diagnosis. The extent of this problem is not known at a regional or

national level but it likely occurs in some cases and places. But this does not involve labeling normal children as having ADHD (over-diagnosis). Of course there is probably over-diagnosis going on by some clinicians in some locales but we have not seen it at a national level, though that is hard to track in the U.S. as we have no nationwide databases. The few studies that examined for this, such as the Great Smokey Mountains epidemiological survey by Duke scientists Jane Costello and Adrian Angold, found that a small percentage of children were diagnosed with ADHD even though they didn't meet all of the DSM criteria for the diagnosis. But even in those few percentage cases of children, it was found that the children so "over-diagnosed" were highly symptomatic and impaired but just didn't have the exact number of symptoms or age of onset demanded by the DSM. The same has been found in some other studies of large regions. In mine and others' opinions, such children should still receive treatment even if "subthreshold" in their symptoms because they are impaired (suffering) and it is impairment that we exist to treat. We have no evidence of widespread diagnosis of normal or typical children as having ADHD, which is really what over-diagnosis means.

©2017, Russell A. Barkley, Ph.D.