The Genetic, Environmental, and Epigenetic Etiology of Antisocial Personality Disorder

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Abstract

Antisocial personality disorder (ASPD) is a cognitive disorder that impairs interpersonal functioning, such as lacking empathy, guilt, and intimacy, while abundantly exploiting, deceiving, dominating, and intimidating to manipulate other people. Such symptoms affect society with danger, violence, and exposure to harm, while individuals with ASPD are often faced with complications of criminal confinement, homicidal and suicidal behavior, low socioeconomic status, comorbidity with other mental health disorders, and early death, typically due to violence. The severity of this dilemma points to the necessity to investigate this disorder's root causes. The following studies discuss the genetic, environmental, and epigenetic risks that prompt the development of the personality disorder. Inheriting certain single-nucleotide polymorphisms, experiencing environmental risk factors (such as childhood adversity), and having gene expression obstructed by methylation may alter cognitive mechanisms and lead to ASPD. There is currently no effective treatment for ASPD yet, but the initial step to advance treatment requires an understanding of its etiology. This literature review will investigate the genetic, epigenetic, and environmental causes of antisocial personality disorder.

Keywords

Antisocial personality disorder, Personality disorders, Genetics, Epigenetics, Environmental causes, Etiology, Childhood adversity, Single-nucleotide polymorphism, Psychology, Biology

Introduction

Antisocial personality disorder (ASPD), commonly known as sociopathy, is a mental disorder that exists in approximately 1-4% of the American population (Mayo Clinic Staff 2019) (Werner et al 2015). The DSM-5 states that the personality disorder has the effects of significant, constant impairments in personality functioning, antagonism, and disinhibition ("DSM-IV" 2012). Interpersonal dysfunction in ASPD involves lacking the ability to empathize or be intimate with others, while self-functioning is impaired by ego-centrism and having self-serving goals that could potentially be unethical ("DSM-IV" 2012). Antagonism is interpreted as manipulation, deceit, callous disregard towards others, lacking remorse about unethical actions, aggression, sadism, and hostility (Mayo Clinic Staff 2019). Finally, disinhibition is defined by irresponsibility, impulsivity, and reckless risk-taking (Mayo Clinic Staff 2019).

Those impairments and effects indicate that antisocial personality disorder may affect society by exposing the general population to violence, exploitation, and harm. It may also burden individuals with the disorder with the consequences of criminal confinement, homicidal and suicidal behavior, low socioeconomic status, the development of other cognitive disorders, and early death, typically due to violence (Mayo Clinic Staff 2019). Although the condition is prevalent in only 1-4% of the American population, the total population as of 2020 is 332.4 million, meaning that 3.3 million to 13.2 million people in the United States may have ASPD (Derick 2022) (Werner et al 2015). With such a vast number of individuals with ASPD, the general population is at risk of facing the consequences of antisocial behavior in the United States. As a personality disorder with effects that can be severe, the cognitive science community must understand the disorder.

Although there is currently no effective treatment or prevention method for ASPD, a step towards advancing prevention methods is understanding the etiology, or cause, of ASPD (Mayo Clinic Staff 2019). The following studies' authors theorize that genetic inheritance from parents, adverse environmental experiences, and epigenetic alterations due to gene-environment interactions contribute to the development of antisocial personality disorder (Philibert et al 2011) (Checknita et al 2015) (Beach et al 2010) (Rautiainen et al 2016) (Barr et al 2020) (Glenn et al 2013). Typical risk factors that will be further elaborated on are having an S allele in the serotonin regulator gene, family history of mental health disorders, childhood and adolescence adverse experiences, exposure to television and brutality, and diagnosis of conduct disorder (CD) before adulthood (Mayo Clinic Staff 2019) (Beach et al 2010) (Glenn et al 2013). This literature review investigates the genetic, environmental, and epigenetic etiology of antisocial personality disorder.

Genetic Causes

Background

Genome-wide association studies (GWAS) are experiments that analyze differences in participants' DNA, which will reveal certain variants related to a trait — in this case, ASPD (Iyegbe and O'Reilly 2022). They single out SNPs — single nucleotide polymorphisms, also known as substitution variations — that reach genome-wide significance (a strong relation) to ASPD. The SNP clusters are identified by their ID number, such as "rs9268528." These studies are very frequently used, successful, and require large samples in the thousands for accurate results (Iyegbe and O'Reilly 2022). Some disadvantages are that it is difficult to identify rare variants linked to a disease and it is complicated to decipher which variants are causal or do not contribute to a phenotype, since it does not explain the actual mechanisms (Iyegbe and O'Reilly 2022). The best one can do with GWAS results is to identify how the mutation may affect the gene's function, and theorize the gene's mechanisms that could potentially lead to the development of ASPD. The following articles are genome-wide association studies pinpointing variations that lead to antisocial phenotypes.

A Genome-Wide Association Study of ASPD

The GWAS conducted by Rautiainen et al. had a sample of 370 (339 (91.6%) males, 31 (8.4%) females) criminals with ASPD, and 5850 (3345 (57.2%) males, 2505 (42.8%) females) healthy people from cohorts in Finland (Rautiainen et al 2016). In total, there were 6220 participants (Rautiainen et al 2016). They split one of the GWAS into a sample of both males and females, while another GWAS was split into a sample of males only, possibly due to the lack of females in this experiment (Rautiainen et al 2016). The cohort of criminals was retrieved from 2010-2011 in Finland prisons, where they were screened for ASPD using DSM-IV and SCID-II diagnostic criteria, then 370 prisoners were randomly selected to be part of the GWAS sample (Rautiainen et al 2016). After discovering certain SNPs related to ASPD, they replicated them and repeated the study to confirm the reliability of those results (Rautiainen et al 2016). The confirming analysis was performed to ensure that those SNPs contributed to ASPD had a total of 173 cases (141 (81.5%) males, 32 (18.5%) females), and 3766 controls (1587 (42.1%) males, 2179 (57.9%) females) (Rautiainen et al 2016).

In the sample of both males and females, 8 SNPs were found to be related to ASPD, and one of the strongest associations was located in the 7p22.2 chromosome, near the *SDK1* gene

in the SNP cluster rs6462756 (Rautiainen et al 2016). However, this locus was considered spurious because no other variant within 500 kilobases (kb) indicated that it was related to ASPD (Rautiainen et al 2016). Besides the false result, the most significant SNP clusters were rs9268528 and rs9268542, which were both on chromosome 6p21.32, intragenic (within) the genes *BTNL2* and *HLA-DRA* (Rautiainen et al 2016). For background, the *HLA-DRA* gene codes the proteins called Human Leukocyte Antigens (HLA), which play a role in the immune system by differentiating foreign substances and the body's substances (Rautiainen et al 2016). The *BTNL2* gene regulates T-cell multiplication in the immune system ("BTNL2"). It is unclear how alteration in these genes affects cognitive mechanisms, as these genes are only known to play a role in the immune system. These SNPs were one of the 8 selected SNPs to be replicated in confirmation later (Rautiainen et al 2016). Other SNP clusters that were somewhat statistically significant and chosen to be replicated were rs2395163 and rs2239804 (Rautiainen et al 2016). Overall, these SNPs in the total sample were a few of the chosen for replication to confirm their correlation with ASPD (Rautiainen et al 2016).

In the sample of males only, the most statistically significant SNP was rs6458146, which was intergenic between the *LINC00951–LRFN2* genes on chromosome 6p21.2 (Rautiainen et al 2016). The *LINC00951* and *LRFN2* genes are expressed in the frontal cortex of the brain, which plays a role in fear conditioning, stress response, and decision making (Raine et al 2000) (Rautiainen et al 2016). Alterations of these genes may lead to poor development of a conscience, antisocial responses to under-stimulation of fear, and risky behaviors, all of which are symptoms of ASPD according to the DSM-5 ("DSM-IV" 2012) (Raine et al 2000) (Rautiainen et al 2016). Several other nearby loci that were statistically significant were rs9471290 (Odds Ratio = 1.68), rs10498746 (OR = 1.72), rs7749170 (OR = 1.67), rs4714329 (OR = 1.56) (Rautiainen et al 2016). These odds ratios (OR) show that there is a strong chance of having ASPD with these SNPs. Altogether, eight SNP clusters from the 6p21 chromosome (6p21.2 and 6p21.32) were chosen for genotyping in the cases and controls to reinvestigate their genetic principles (Rautiainen et al 2016).

After the replication, the originally tested genotypes and the retested genotypes had a 99% similarity, proving the accuracy of these results (Rautiainen et al 2016). SNPs in the 6p21.2 band subdivision of the chromosome had consistent results and the replication confirmed that rs4714329 (OR = 1.75) reached the most genome-wide significance concerning having ASPD, closely followed by rs9471290 (OR = 1.40) (Rautiainen et al 2016). However, the most significant SNPs in the 6p21.32 chromosome were reversed in comparison to the original GWAS trial, with rs9268528 being the leading SNP in this band subdivision (Rautiainen et al 2016). That variant was not as significantly correlated with ASPD, possibly due to the high levels of polymorphism in the genomic region (*HLA-DRA*) and lack of power from insufficient sample size (Rautiainen et al 2016). Compared to the next GWAS study, Barr et al. had more than twice the sample size of Rautiainen et al.'s. Thus, these results could have been more accurate if the sample size had been larger. The alleles at *HLA-DRA* had high levels of polymorphism, indicating that multiple SNPs working simultaneously in that region could have contributed to ASPD (Rautiainen et al 2016). This can compare to identifying a honking car in a high-traffic area — if someone honks in a group of other honking vehicles, it's nearly impossible to find out which one contributes the most to traffic noise. In GWAS, it's equally difficult to find out which SNP in an area dense with SNPs has the most impact on ASPD. Thus, the 6p21.32 chromosome had less genome-wide significant results.

The replication trial was a crucial way to ensure the reliability of the first trial, because of the slightly different results discovered in 6p21.32 (Rautiainen et al 2016). This study could have furthered their confirmations by doing another replication trial for good measure. Another way Rautiainen et al. clarified that those 8 key SNPs were associated with ASPD was by analyzing criminals without ASPD but may have been close to the diagnosis requirements (Rautiainen et al 2016). As a result, the participants without ASPD had no significant association with those SNPs, confirming that those SNPs did, indeed, correlate with antisocial personality disorder (Rautiainen et al 2016).

Overall, variants in the vicinity of 6p21.2 were strongly correlated with ASPD, while the variants in 6p21.32 were still correlated but with less statistically significant results, due to the inability to pinpoint which SNP in that region contributes the most to ASPD (Rautiainen et al 2016). The strongest variation found was rs4714329 from the *LINC00951* gene (Rautiainen et al 2016). *LINC00951* causes signals linked to antisocial personality, thus, a polymorphism in this area (i.e. rs4714329) may hinder or enhance these signals (Rautiainen et al 2016). Several other confirmed risk variants were rs4714329, rs2395163, rs9268528, rs9268542, and more from 6p21.2 and 6p21.32 (Rautiainen et al 2016).

Uncertainty in these results lies in the genomic region, 6p21.32, because the replication showed different results than the original GWAS – rs9268528, rs9268542, rs2395163, and rs2239804 changed in genome-wide significance, indicating that their correlations with ASPD may not be as strong or consistent (Rautiainen et al 2016). Although this was speculated to be due to how rich the region is with SNPs rather than an error in their method, further investigation into this region's link with ASPD would have clarified its variants' genome-wide significance. Another uncertainty lies in a variant considered spurious – rs6462756, near the *SDK1* gene – because it was the only locus that gave a signal from the 7p22.2 genomic region while other SNPs were found in groups in the same genomic regions (Rautiainen et al 2016). This indicates that it was a false positive (Rautiainen et al 2016). Thus, this GWAS identified and confirmed eight SNPs from the 6p21.2 and 6p21.32 regions by extensively comparing Finnish criminals with ASPD and healthy controls (Rautiainen et al 2016).

A Family-Based Genome-Wide Association Study of Externalizing Behaviors

Like the previous study, this genome-wide association study identified specific SNPs that led to externalizing behavior in general, including ASPD (Barr et al 2020). The meta-analysis sample had a total number of 15,112 participants (Barr et al 2020). Participants were assessed by DSM-IV criteria for ASPD, while for individuals under 18, DSM-III-R assessed conduct disorder (CD) criteria (Barr et al 2020). Assessment of CD was due to minors who were ineligible to be diagnosed with ASPD and being diagnosed with conduct disorder as a child or adolescent is a large predictor of ASPD in adulthood ("DSM-IV" 2012) (DeLisi et al 2019). The researchers also used externalizing scores to measure the type of their externalizing behavior (Barr et al 2020). Although this meta-analysis covered other externalizing behaviors too (such as drug and alcohol abuse), this review focuses on the aspect of ASPD.

Results showed that there were 3 significant SNPs associated with general externalizing behaviors (Barr et al 2020). The most genome-wide significant variant is rs2376620 ($P = 3.91\times10^{-9}$), which was on Chromosome 6 the *CDKN1A* (cyclin-dependent kinase inhibitor 1A) gene (Barr et al 2020). The extremely small P-value proved that this variant strongly contributed to externalizing behaviors, including ASPD (Barr et al 2020). The *CDKN1A* gene produces a protein that responds to stress stimuli; thus, this variant may disrupt one's ability to respond to

stress and lead to antisocial or externalizing behavior ("CDKN1A"). This locus was more significantly associated with EA families ($P = 2.43\times10^{-8}$) than AA families ($P = 0.009$), which could be since the EA sample size was approximately twice as large as AA, making rs2376620 appear more often in the larger sample (Barr et al 2020). The next most significant SNP concerning externalizing behaviors was rs2433198 ($P = 1.78\times10-8$), located on Chromosome 15, in the locus: *GCOM1/MYZAP* (GRINL1A complex locus/myocardial zonula adherens protein) (Barr et al 2020). This combined locus codes proteins that allow transcription of other genes, but it does not appear to affect any other mechanisms ("GCOM1"). Thus, modifications of this locus may lead to transcription errors in other genes that are relevant to ASPD. Rs2433198 was prevalent in both EA ($P = 8.75\times10^{-6}$) and AA families ($P = 2.86\times10^{-4}$), indicating that it had a strong relation to externalizing disorders among families of different ancestries (Barr et al 2020). The final genome-wide significant SNP is rs12928255 ($P = 1.93\times10^{-8}$), located on Chromosome 16, in the *PKD1L2* gene (Barr et al 2020). *PKD1L2* is a pseudogene — unable to code proteins — indicating an unclear relationship between rs12928255 and ASPD ("PKD1L2") ("Pseudogene"). This finding was also consistent with families of European ($P = 1.26\times10^{-7}$) and African ancestries ($P = 0.024$) (Barr et al 2020).

These three SNPs were in Expression Quantitative Trait Loci (eQTL) interactions with genes, meaning that they only explained a part of the genetic etiology of externalizing behavior and nearby genes also contributed to the phenotype by interacting with the genes containing those SNPs (Nica and Emmanouil 2013) (Barr et al 2020). This explains how the *GCOM1/MYZAP* locus was involved with ASPD, although it only affected transcription — theoretically, it must have interfered with the transcription of nearby genes that directly affected cognitive behavior, leading to the development of ASPD and other externalizing disorders (Nica and Emmanouil 2013) (Barr et al 2020). The same idea could be applied to *PKD1L2* — the pseudogene must have had an active mRNA and regulated the transcription of other genes that directly affected externalizing disorders.

Overall, these 3 SNPs were observed in EA and AA families to be related to externalizing behavior, including ASPD (Barr et al 2020). However, they stated that their results were not robust enough to replicate and confirm their findings, meaning that these variants may not be reliable (Barr et al 2020). Even though this sample size was more than twice of Rautiainen et al.'s sample, the sample size was not considered large enough — it needed to be in the hundreds of thousands, not the tens of thousands — to be significantly related to externalizing disorders (Rautiainen et al 2016) (Barr et al 2020). Thus, this study could have improved the accuracy of its results by upgrading its sample size to replicate and confirm some variants. Therefore, these 3 genome-wide significant SNPs — rs2376620, rs2433198, and rs12928255 — may increase the risk of externalizing behaviors, including ASPD (Barr et al 2020).

Environmental Causes

Background

Criminology research has shown that abuse, neglect, and adverse experiences in children have led to lifelong mental health and behavioral issues (DeLisi et al 2019). If adverse experiences are accumulated, the most extreme, violent, and chronic criminality may result in an individual (DeLisi et al 2019). All the following studies investigate the genetic and environmental etiology of ASPD, which is what this study will inspect (DeLisi et al 2019).

A Study on the Effect of Childhood Adversity and Psychopathology on ASPD

As one of the most impactful personality disorders found in serious criminals, DeLisi et al. found it vital to understand how genetics and environmental influences lead to ASPD (DeLisi et al 2019). From a total of 863 incarcerated participants with ASPD from Midwestern U.S., 84% (n = 725) were male while 16% (n = 138) were female, 79.4% (n = 685) were Caucasian while 20.6% (n = 178) were African American, and 92% (n = 794) were non-Hispanic, while 8% (n = 69) were Hispanic (DeLisi et al 2019). The mean age of all participants was 44 years (DeLisi et al 2019). The types of offenses of this sample were drug offenses at 61.1%; firearm felonies at 13%; bank fraud, money laundering, and identity theft at 13%; child pornography at 6.5%; and the remaining 6.4% of offenses unspecified (DeLisi et al 2019). DeLisi et al. measured the Relative Risk Ratio (RRR) of being diagnosed with ASPD compared to people without a certain variable and Z-score, which is how many standard deviations away the data point is from the mean (DeLisi et al 2019) ("Z-Score"). The subjects were compared to each other by their ASPD status — whether they had symptoms only, were officially diagnosed, or had no evidence of ASPD. This could have been to show how certain variables may link to symptoms only, diagnosis of ASPD, both, or neither (DeLisi et al 2019). They also separately investigated each specific type of adverse experience (i.e. mother neglect, physical abuse, etc.), and cumulative childhood adversity.

Results demonstrated that childhood adversity is associated with ASPD symptoms, though with slightly different outcomes (DeLisi et al 2019). For instance, subjects with conduct disorder with an RRR of 3.09 (3.09 times more likely than people without CD) and a Z-score of 3.12 (which greatly deviates from the mean, considering it an anomaly) often ended up with ASPD symptoms (DeLisi et al 2019). Similarly, people with early-onset arrests had an RRR of 0.92 (slightly less likely than people without early arrests) and a Z-score of -2.44 (meaning that this probability is slightly far away from the mean), also leading to ASPD symptoms (DeLisi et al 2019). Lastly, physical abuse (RRR = 1.51, z = 2.22), with a 51% higher risk than individuals without that variable, was also positively correlated with symptoms (DeLisi et al 2019). Overall, symptoms of ASPD are most strongly correlated with conduct disorder, physical abuse, and early-onset arrest (DeLisi et al 2019).

In contrast, formal ASPD diagnosis was mostly from adverse childhood experiences only, but conduct disorder and arrests remained associated (DeLisi et al 2019). For instance, CD had an RRR of 11.46 for ASPD diagnosis with a Z-score of 6.92 (DeLisi et al 2019). Although this seems like an outlier, this result could be due to the degree of overlap between the symptoms of CD and ASPD — the main difference between them is that conduct disorder is a diagnosis for minors only (DeLisi et al 2019) (Rockville et al 2016). Arrest onset had a very close RRR of 0.94 for diagnosis with a Z-score of -3.06, also indicating that this data could be an outlier (DeLisi et al 2019). Out of individual adverse experiences, sexual abuse had the greatest RRR of 1.69 (Z = 2.02) (DeLisi et al 2019). Overall, the strongest adverse experiences leading to symptoms of ASPD are CD, early-arrest onset, and physical abuse (DeLisi et al 2019). The strongest adverse experiences leading to the formal diagnosis of ASPD were CD, arrest onset, and sexual abuse (DeLisi et al 2019). Other psychopathological illnesses and behavioral conditions like ADHD, expulsion from school, and alcohol abuse had no significant correlations with either symptoms or official diagnosis, concluding that childhood adverse experiences have a greater impact on ASPD than psychopathology (DeLisi et al 2019).

Table 1: ASPD Symptoms and Variables

The correlation between other psychopathological illnesses, individual, and cumulative adverse childhood experiences, and ASPD symptoms (DeLisi et al 2019).

Variable	RRR	z
Adverse childhood experiences (cumulative)	0.99	-0.22
Physical abuse (individual)	1.51	2.22
Sexual abuse (individual)	1.33	0.83
Conduct disorder (cumulative)	3.09	3.12
Arrest onset (cumulative)	0.92	-2.44

Table 2: ASPD Diagnosis and Variables
The correlation between other psychopathological illnesses, individual, and cumulative adverse childhood experiences, and ASPD diagnosis (DeLisi et al 2019).

Variable	RRR	z
Adverse childhood experiences (cumulative)	1.09	2.48
Physical abuse (individual)	0.91	-0.34
Sexual abuse (individual)	1.69	2.02
Conduct disorder (cumulative)	11.10	6.92
Arrest onset (cumulative)	0.94	-3.06

Tables 1 and 2 portray the correlation between each variable and antisocial symptoms, and each variable and the diagnosis of ASPD. Most variables have greater RRRs of diagnosis than symptoms, with only one exception of physical abuse (DeLisi et al 2019). This concludes that childhood adversity had a greater impact on the official diagnosis than only having symptoms of ASPD (DeLisi et al 2019). DeLisi et al. speculate that experiencing physical abuse is a significant predictor of ASPD symptoms because it leads to hostility, scorn, skepticism of adult authority, irritability, aggression, and carelessness about others (DeLisi et al 2019). On the other hand, sexual abuse may be a significant predictor of ASPD diagnosis because the severity of the condition may lead to the worst adjustment problems (DeLisi et al 2019). CD and arrest onset are variables that could cause both symptoms and diagnosis if experienced before adulthood (DeLisi et al 2019).

The discussion of this study also touches on the probability of genetic inheritance of ASPD (DeLisi et al 2019). Vaughn et al. uncovered from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) that 70% of ASPD-diagnosed subjects had nearly no family history of the disorder, 9% had behavioral patterns in parents and offspring, and 21%

had a family history dating back multiple generations of behavior problems, criminality, and violence (Vaughn et al 2014). In the *de novo* (appearing for the first time) instances of antisocial personality disorder, sexual abuse was theorized to be the leading cause of the disorder's diagnosis (DeLisi et al 2019). Sexual abuse was also the main root of multigenerational ASPD being inherited (DeLisi et al 2019). CD and arrest onset correlated with both symptoms and diagnosis, physical abuse correlated mostly to symptoms, and sexual abuse was strongly associated with diagnosis (DeLisi et al 2019). After inheriting the disorder, there is a great risk of the cycle of adversity repeating in the household along with more felonies, aggravated assault, domestic assault, and other forms of assault (DeLisi et al 2019). This study hypothesized that childhood adversity experiences with frequency counts would show different correlations with ASPD, which is something another study in the future should consider (DeLisi et al 2019). Overall, DeLisi et al.'s results reveal forms of childhood adversity and psychopathology — including abuse, conduct disorder, and early-onset arrests — that are significant environmental predictors of symptoms and diagnosis of ASPD (DeLisi et al 2019).

A Review on ASPD

While genetics make up approximately half of the influence on antisocial behavior variance, this implies that the remaining half is due to environmental or epigenetic influences (Ferguson 2010) (Glenn et al 2013). This review on ASPD discussed several studies inquiring about the environmental etiology of ASPD (Glenn et al 2013). A study on television that spanned 26 years with 1037 participants from New Zealand discovered that young adults had significantly higher chances of criminality and diagnosis of ASPD when they spent most of their adolescence and childhood watching the television (Glenn et al 2013) (Robertson 2013). Variables that were strictly controlled were sex, intelligence quotient (IQ), socioeconomic status, previous antisocial conduct status, and parental maintenance quality (Glenn et al 2013) (Robertson 2013). They speculated that this correlation between TV and ASPD was due to the observational learning theory, in which humans imitate and internalize actions seen on television, leading to the desensitization towards brutality, the development of aggressive behavior, reduced social interaction, poorer education, and the increased probability of unemployment (Glenn et al 2013) (Robertson 2013). Thus, TV viewing is an environmental factor that can potentially contribute to the development of ASPD (Glenn et al 2013) (Robertson 2013).

Another significant predictor of ASPD in adulthood was the quality of care in an individual's early life, especially from their mother (Shi et al 2012) (Glenn et al 2013). For instance, early maternal withdrawal by interacting too silently and the lack of personally soothing and greeting the infant often contributed to ASPD by inducing disorganized attachment (Shi et al 2012) (Glenn et al 2013). Furthermore, Kumari et al. hypothesized that psychosocial deprivation contributes to an abnormal brain structure, which was frequently found in subjects with ASPD (Kumari et al 2012) (Glenn et al 2013). This study consisted of 56 males (26 had ASPD or a history of violence, while 30 were not violent), all of whom were assessed on psychosocial deprivation by medical imaging (Kumari et al 2012) (Glenn et al 2013). The researchers recognized that psychosocial deprivation, such as neglect and abuse, decreased the prefrontal cortex and inferior frontal region of the brain in all subjects, and decreased the thalamus in ASPD subjects (Kumari et al 2012) (Glenn et al 2013). Consequently, a smaller prefrontal cortex and inferior frontal region could lead to trouble with behavioral control, inhibition (self-consciousness), and the ability to make reasonable decisions, while a deficit in the thalamus volume could induce difficulty in extinguishing intrusive thoughts and memories related

to preceding mistreatment (Kumari et al 2012) (Glenn et al 2013). To note, a decrease in the prefrontal cortex and inferior frontal region appeared in both violent and non-violent participants (Kumari et al 2012) (Glenn et al 2013). This showed that psychosocial deprivation had a smaller correlation to ASPD and it did not always lead to criminal behavior, since more than half of the participants did not have a history of violence (Kumari et al 2012) (Glenn et al 2013). As mentioned before, genetic adjustments from the *LINC00951* gene in the frontal cortex of the brain may lead to the poor development of a conscience, antisocial responses to under-stimulation of fear, and risky behaviors, all of which are symptoms of ASPD according to the DSM-5 ("DSM-IV" 2012) (Raine et al 2000) (Rautiainen et al 2016). This highlights how both environmental (i.e. psychosocial deprivation) and genetic (i.e. mutations) factors affect similar mechanisms in the brain, leading to ASPD. Overall, the most significant studies mentioned in this review revealed that television, maternal withdrawal, and psychosocial deprivation are environmental risks for developing ASPD (Glenn et al 2013).

Epigenetic Causes

Background

Epigenetics, though insufficiently investigated when examining the etiology of a disease or disorder, plays a predominant role in developing ASPD. The epigenome is a collection of chemical tags — such as methyl, acetyl, phosphoryl, and ubiquitin, — that edit gene expression without changing the DNA ("Epigenome at a Glance"). These chemical tags attach to DNA wrapped around histones — proteins that organize the DNA — and onto the histones themselves ("Epigenome at a Glance") ("Gene Control"). Once methyl tags affix to the cytosine base, it will be nonviable for the mRNA to transcribe that particular region of the DNA due to blockage, leading to gene silencing ("Gene Control"). The following studies focus on the methylation and gene silencing interposing mechanisms, leading to ASPD. The epigenome adapts and responds to environmental stimuli, such as diet, social interactions, physical activities, and stress ("Epigenome at a Glance") ("Epigenome Learns"). It also responds to cell signals, such as direct contact, released, and hormonal signals ("Epigenome Learns"). These signal functions performed by gene regulatory proteins activate or deactivate specific genes and summon enzymes to add or subtract epigenetic tags on the genome ("Epigenome Learns"). As the body endures more of these experiences, the epigenome will learn how to regulate gene activity and increase its epigenetic profile – the set of tags that affect gene expression ("Epigenome Learns"). The epigenome usually lasts throughout an individual's lifetime and may even pass on to offspring ("Genomic Imprinting") ("Epigenetics & Inheritance"). Reprogramming is the process in which the zygote eliminates the epigenome for a fresh start ("Epigenetics & Inheritance"). However, there is a chance of the epigenome surviving the process of reprogramming through a process called imprinting, which 1% of the genes experience ("Epigenetics & Inheritance") ("Genomic Imprinting"). Thus, some epigenetic tags will pass onto the offspring, leaving certain genes deactivated or activated. This indicates that epigenetic factors that increase the risk of ASPD in a parent may pass onto offspring. In summary, the epigenome is the effect of environmental factors that may change gene expression without directly changing the genome. How do these epigenetic mechanisms apply to the development of antisocial personality disorder?

A Study on the Epigenetics of *MAOA* and ASPD

A study on gene-environment interactions on the Monoamine Oxidase A (MAOA) transcriptional enhancers – DNA sequences that allow binding for transcription – discovered its association with ASPD (Philibert et al 2011) (Shlyueva et al 2014). Monoamine Oxidase A is an enzyme involved in the catabolism of monoamine neurotransmitters, such as serotonin (Philibert et al 2011). The *MAOA* gene has 15 exons – parts of the genome that end up being transcribed – that cause 2 splice variants – variations that occur at the border of introns and exons, possibly interrupting mRNA splicing (Philibert et al 2011). Philibert et al. discovered a Variable Nucleotide Tandem Repeat (VNTR) – an area of DNA with repeated nucleotides – whose methylation strongly correlated to child abuse and ASPD, labeling it "*MAOA* P2" (Guilherme et al 2011) (Philibert et al 2011). Another regulatory motif — a brief DNA pattern that controls gene expression — of the *MAOA* gene was labeled "*MAOA* P1" (Philibert et al 2011) (Kellis et al 2021). As a result of these two regulatory motifs, gene expression regulation was theorized to relate to behavioral illnesses like ASPD, while the epigenome was theorized to have formed from strong gene-environment interactions with others' antisocial behaviors (Philibert et al 2011). Thus, Philibert et al. theorized that individuals may inherit ASPD epigenetically by exposure to environmental risk factors that impact gene expression (Philibert et al 2011).

This study uses samples from the Iowa Adoption Studies (IAS) with procedures authorized by the University of Iowa Institutional Review Board (Philibert et al 2011). The researchers evaluated symptoms of ASPD in the 571 total participants in the sample by using the DSM-III, DSM-IV, and Feighner Research Diagnostic Criteria (RDC) (Philibert et al 2011). They focused on each subject's effect of child abuse, including corporal punishment by parents and sexual abuse by relatives (Philibert et al 2011). Out of the 571 total participants, 259 (45.36%) were males and 312 (54.64%) were females (Philibert et al 2011). 93.7% of the sample was White, 2.45% was African American, 2.45% was Hispanic, 0.35% was American Indian, 1.05% was other, and 0% was Asian (Philibert et al 2011). Unlike DeLisi et al. 's sample, they included *Hispanic* as a race option, rather than splitting the sample between races and ethnicities (DeLisi et al 2019) (Philibert et al 2011). The process of DNA sequencing – examining the order of nucleotides – was performed by the University of Iowa DNA Facility (Philibert et al 2011). Philibert et al. investigated the specific effects of *MAOA* P1 and *MAOA* P2 on ASPD (Philibert et al 2011).

As for the results, a common pattern they observed in the sample was the 2 different decamer repeat units in the *MAOA* P2 region (Philibert et al 2011). The first repeat unit (A) had a pattern of CCCCTCCCCG, while the second unit (B) had a pattern of CTCCTCCCCG (Philibert et al 2011). As shown, B has a polymorphism from cytosine to thymine at the base pair 6365508 (Philibert et al 2011). In the first 6 repeat units (60 base pairs) of the genomic region in all subjects, their decamers followed an ABABAB pattern (Philibert et al 2011). For the 7th repeat unit (7R), the DNA sequences followed an ABABABA structure, then the 8R followed an ABABABAA structure, 9R had an ABABABAAA pattern, followed by 10R with an ABABABAAAA sequence (Philibert et al 2011). As for the *MAOA* P1 VNTR, the study did not clarify the sequences that were present in this region. The sequences in *MAOA* P2 were studied by haplotype distribution (the comparison of genetic patterns) in comparison with *MAOA* P1 sequences, gene expression, and ASPD characteristics (Reddy et al 2017) (Philibert et al 2011).

According to the haplotype distribution, 136 diagnosed subjects with the 4-repeat (4R) genotype from *MAOA* P1 also carried the 9R genotype from *MAOA* P2, indicating that carrying

those genotypes from both VNTR regions simultaneously could contribute to antisocial personality disorder (Philibert et al 2011). As shown in Table 3, 46 people had 3R genotypes from P1 along with the 7R-11R genotypes from P2, pointing to a small correlation with ASPD (Philibert et al 2011). This means that there was a slight chance of ASPD being due to having that combination of genotypes. Taking into account genotypes from both *MAOA* regions could impact the identification of ASPD — for instance, scientists considered the severity of ASPD in a participant low by looking at their P1 genotype only, but they found the opposite when involving the P2 genotype (Philibert et al 2011). Thus, both *MAOA* P1 and P2 regions were necessary to evaluate simultaneously when determining the degree of ASPD (Philibert et al 2011).

Table 3: Observed Individuals with ASPD with Gene Combinations from *MAOA* P1 and P2
The number of observed individuals with a certain genotype combination from *MAOA* P1 and P2 simultaneously (Philibert et al 2011).

P1 Genotype	P2 Genotype	Observed Individuals
2R	10R	1
3R	8R	2
3R	9R	17
3R	10R	46
3R	11R	13
3.5R	9R	6
4R	9R	136
5R	9R	1

The P2 sequences were analyzed for possible enhancement — the upregulation of transcription and gene expression — while the promoter regions — regions of DNA where proteins attach onto to prompt transcription — were scanned for gene activity leading to ASPD (Philibert et al 2011) (“Promoter 2022”). The first promoter scan analysis showed that P2’s 9R and 10R alleles led to more gene activity than the 8R and 11R alleles (Philibert et al 2011). This could mean that the epigenetic silencing of 8R and 11R could lead to dysfunction of the MAOA enzyme, which is supposed to break down monoaminergic neurotransmitters like serotonin (Philibert et al 2011). Without the MAOA enzyme being produced, the lack of catabolism in certain chemicals essential for behavioral functions may lead to ASPD behaviors. However, the luciferase transfection assessments, which are tests to see whether a protein regulates gene transcription, showed slightly different results (Philibert et al 2011) (Kroemer). The transfection assessment revealed that the 9R allele was the most expressed, 8R and 11R had median activity, and 10R had the least expression (Philibert et al 2011). This could mean that the epigenetic silencing of 9R could lead to dysfunction of the MAOA enzyme, which is supposed to break down monoaminergic neurotransmitters like serotonin (Philibert et al 2011). Without the MAOA enzyme being produced, the lack of catabolism in certain chemicals essential for behavioral functions may lead to ASPD behaviors. Silencing the following 8R and 11R alleles may have led to the same dysfunction in behavioral mechanisms, but not as likely, as the transfection assessments show. To summarize, the methylation of the 10R allele has the highest

probability of interposing MAOA enzyme productions, causing behavioral issues and ASPD symptoms (Philibert et al 2011). This means that in P2 only, the 10R allele has the most significant effect on the *MAOA* gene and ASPD (Philibert et al 2011). Additionally, childhood abuse is highly associated with *MAOA* modification for adulthood ASPD, which will be elaborated on in another study (Philibert et al 2011) (Beach et al 2010).

Overall, Philibert et al. discovered that ASPD phenotypes are derived from the *MAOA* P1 and P2 VNTRs (Philibert et al 2011). While the *in silico* (software) analyses hypothesized that both 9R and 10R would enhance the transcription of *MAOA* equally, experimental results proved that the 10R genotype was the most methylated, disrupting binding sites for transcription, lowering enhancement and gene expression, downregulating monoaminergic neurotransmitters levels, and therefore, causing antisocial behavior (Philibert et al 2011). With P2 being more impactful in *MAOA* transcription than P1, one can conclude that methylation at 10R of P2 has a significant effect on ASPD development (Philibert et al 2011). However, these results mostly apply to middle-aged White subjects only because the sample was primarily White and in their late 40's (Philibert et al 2011). As shown, 93.7% were White, 2.45% were African American, 2.45% were Hispanic, 0.35% were American Indian, 1.05% were other, and 0% were Asian (Philibert et al 2011). This exposes the lack of diversity in the sample, which is an aspect future studies should avoid in genotyping. Expanding the racial and age diversity of this sample may have contributed to findings of different DNA sequences, methylated alleles, and conclusions (Philibert et al 2011).

A Study on the Methylation of MAOA in Male Criminals with ASPD

Like the previous study, Checknita et al. strived to explain the associations between *MAOA* regulation, serotonin regulation, and ASPD in criminals (Checknita et al 2015). By comparing the whole-blood DNA of 86 male offenders with ASPD (all diagnosed under DSM-IV guidelines) with 74 healthy controls, they discovered that insufficient *MAOA* gene activity leads to serotonergic system dysfunction and antisocial personality (Checknita et al 2015). Checknita et al. found extreme hypermethylation of the *MAOA* promoter region and decided to duplicate their Region of Interest (ROI), which was 678 base pairs long, to see the functional impact of the hypermethylation on gene expression in the cases (Checknita et al 2015). They realized that hypermethylation in this ROI led to blockage of transcription factors — proteins that transcribe DNA into mRNA — and downregulated transcription levels (Checknita et al 2015). Another observation worth noting is that the ASPD cases often had much greater quantities of methylation at CpG sites — parts of the genome where guanine follows cytosine in the 5' → 3' direction of DNA — compared to the healthy controls (Checknita et al 2015). Like the previous study, this one also used luciferase assessments to examine gene activity in the replicated ROIs (Philibert et al 2011) (Checknita et al 2015). This study's luciferase assessments revealed that the unmethylated construct (duplicated artificial DNA) of the ROI had 12 times the level of luciferase reporter activity compared to the original ROI construct in the cases with ASPD, while the fully-methylated construct had a 53% decrease in luciferase reporter activity compared to the native ROI construct (Checknita et al 2015). This indicates that methylation in the ROI substantially prohibited gene expression and MAOA enzyme activity, while unmethylation in the same locus upregulated gene expression and MAOA levels. Thus, the methylation levels in the identified Region of Interest (678 bp) significantly affected MAOA levels and behavior characteristics of ASPD (Checknita et al 2015).

The MAOA enzyme contributes to regulating serotonin levels and aggression, thus, one may expect that the deficiency of MAOA may lead to a deficiency of serotonin (Checknita et al 2015). Interestingly, Checknita et al. theorized that there would only be a deficiency of 5-HT (serotonin) in the central nervous system, but to manage an equilibrium, there will be an unexpected increase in 5-HT levels in the blood, leading to increased aggression (Comai et al 2012) (Moffitt et al 1998) (Checknita et al 2015). Although the specific mechanism of this unexpected association is not yet understood, this unexpected phenotype indicates a vaster system contributing to 5-HT levels, which is something for future studies to investigate (Checknita et al 2015). Thus, this study's findings indicate that hypermethylation of the *MAOA* gene leads to decreased MAOA enzymatic production, decreased serotonin levels in the central nervous system, and contrarily, increased serotonin levels in the blood of individuals with ASPD (Checknita et al 2015).

Nevertheless, the results may not have been accurate due to the use of whole blood in substitution for extracting brain tissue, but this could not have been avoided since the participants were living and the option of using brain tissue was unavailable (Checknita et al 2015). There was also no confirmation for the theory of blood 5-HT levels in the case being higher than the healthy cohort because this experiment never assessed the control's 5-HT levels. Since Checknita et al. theorized 5-HT levels being higher in the blood of people with ASPD based on other papers, this flaw indicates that their theory is not supported by their results. Lastly, this study did not have a clear answer about whether *MAOA* methylation was directly associated with ASPD or mediated by environmental experiences, such as childhood adversity (Checknita et al 2015). They only observed how hypermethylation led to ASPD, but they never inspected the causes of hypermethylation (Checknita et al 2015). The next study confirmed that methylation of a similar gene mediated environmental adversities and the development of ASPD by investigating serotonin levels among women with ASPD (Beach et al 2010).

A Study on Methylation of *5HTT* Mediating the Impact of Childhood Sex Abuse on ASPD in Women

Serotonin (5-HT) is a monoamine neurotransmitter that impacts mood, sensory processing, cognition, and sleep (Cornelius et al 2014). The serotonin transporter protein (5-HTT) regulates serotonergic levels (Cornelius et al 2014). By investigating women diagnosed with ASPD from the Iowa Adoptee Study, Beach et al. discovered the correlation between hypermethylation of the *5HTT* gene, serotonin levels, childhood sex abuse, and ASPD in females (Beach et al 2010). All 155 female participants were evaluated for ASPD using DSM-III-R guidelines, DSM-IV guidelines, and Feighner Research Diagnostic Criteria (RDC) (Beach et al 2010). Subjects were also assessed for childhood sex abuse by being asked about such experiences before 16 years of age (Beach et al 2010). To test the methylation of the *5HTT* gene, DNA was extracted from lymphoblast cell lines infected with Epstein Barr Virus (EBV), which is a virus that causes the body to overproduce lymphocytes ("Epstein-Barr" 2020) (Beach et al 2010).

Cornelius et al. explained that individuals with an S allele in the serotonin transporter-linked polymorphic region (5-HTTLPR) are 2-2.5 times more likely to downregulate serotonin transcription compared to an L allele, heightening the risk of several personality disorders (Cornelius et al 2014). The study hypothesized that people carrying the S allele may respond to the downregulation of *5HTT* expression by showing behavioral traits from ASPD

(Beach et al 2010). The results reported that 15 participants (9.68%) had experienced childhood sex abuse (Beach et al 2010). Out of the total sample, 25 (16%) were homozygous for the S allele, 71 (46%) were heterozygous for the S allele, and 59 (38%) were homozygous for the L allele (Beach et al 2010). Although there was a small positive correlation directly between childhood sex abuse and ASPD in women, there were extreme positive correlations between child sex abuse and *5HTT* methylation levels along with *5HTT* methylation and ASPD symptoms (Beach et al 2010). This indicates that while childhood sexual abuse was not directly related to ASPD, it was directly associated with *5HTT*, which could cause ASPD among other personality disorders (Beach et al 2010). The reason why childhood sexual abuse may not be directly related to ASPD in females is that *5HTT* methylation may cause various personality and mood disorders, such as major depressive disorder and alcohol dependence (Cornelius et al 2014). These associations verify the hypothesis that methylation at *5HTT* mediates the association between childhood sexual abuse and ASPD in women (Beach et al 2010).

Beach et al. also tested to see if the *5HTT* genotype “moderated” the impact of methylation on ASPD behavior or affected the association strength between the epigenome and ASPD behavior (2011). They hypothesized that certain S and L alleles moderate the influence of methylation on behavior, which was proven true (Beach et al 2010). This means that if a subject has the S allele, the risk of ASPD development increases, which is often triggered by the methylation of *5HTT* (Beach et al 2010). People having homozygous S alleles had the highest correlation coefficient (r (Shi et al 2012) = 0.573) between methylation and ASPD symptoms compared to people with heterozygous alleles (r (71) = 0.269) and homozygous L alleles (r (59) = 0.143). Therefore, people with methylation in the *5HTT* gene will most likely develop symptoms of antisocial personality disorder if they carry the S allele (Beach et al 2010). This authenticates the hypothesis that the probability of having ASPD due to *5HTT* methylation is moderated by the S and L alleles.

In summary, this study revealed that sexual abuse during childhood leads to the methylation of the *5HTT* gene, perhaps due to the stress it induces from the environment (Beach et al 2010). Then, the epigenetic effect may lead to ASPD (and other cognitive disorders) by dysregulating serotonergic levels (Beach et al 2010) (Cornelius et al 2014). Evidence suggests that homozygous S alleles create the strongest relationship between the epigenome and antisocial behavior (Beach et al 2010). In the overall picture, *5HTT* mediates the relationship between childhood sexual abuse and antisocial personality disorder in females.

Discussion

After delving into numerous studies about the etiology of antisocial personality disorder, many show similar results. The first GWAS study by Rautiainen et al. discovered 8 single nucleotide polymorphisms from the 6p21.2 and 6p21.32 chromosome regions that were strongly associated with antisocial personality disorder in criminals in Finland (Rautiainen et al 2016). An error in their experiment was that they discovered a spurious locus — rs6462756 in the 7p22.2 chromosome (Rautiainen et al 2016). This locus was ruled a false positive because it was the only locus that indicated a relationship with ASPD from its region, indicating that it could have been a mistake (Rautiainen et al 2016). Some other verified SNPs related to ASPD were in genomic regions rich in other SNPs, such as 6p21.32 (Rautiainen et al 2016). However, having too many SNPs in one place made it difficult for the GWAS technology to pinpoint which exact locus contributed the most to ASPD (Rautiainen et al 2016). This led to reversed results of genome-wide significant SNPs from the 6p21.32 region, indicating that their initial results were

slightly different (Rautiainen et al 2016). Although the study already ensured the credibility of their results by performing one replication trial, performing another replication of those SNPs from 6p21.32 would confirm which specific ones are the most genome-wide significant (Rautiainen et al 2016). Despite the varied statistical significance in the SNPs' relationships with ASPD from 6p21.32, the SNPs from 6p21.2 were consistent and still genome-wide significant in the replication trial (Rautiainen et al 2016). Thus, the 8 identified SNPs are shown to be strongly related to ASPD, so having those variations may put an individual at risk of developing the personality disorder (Rautiainen et al 2016). Possessing one of these variants may be a predictor of developing ASPD because it may alter one's cognitive mechanisms (Rautiainen et al 2016). For instance, rs6458146 from chromosome 6p21.2 was intergenic with the *LINC00951* and *LRFN2* genes (Rautiainen et al 2016). The *LINC00951* and *LRFN2* genes are expressed in the frontal cortex of the brain, which plays a role in fear conditioning, stress response, and decision making (Raine et al 2000) (Rautiainen et al 2016). Alterations of these genes may lead to poor development of a conscience, antisocial responses to under-stimulation of fear, and risky behaviors, all of which are symptoms of ASPD according to the DSM-5 ("DSM-IV" 2012) (Raine et al 2000) (Rautiainen et al 2016). Additionally, rs9268528 and rs9268542 were intragenic (within) the genes *BTNL2* and *HLA-DRA* (Rautiainen et al 2016). For background, the *HLA-DRA* gene codes the proteins called Human Leukocyte Antigens (HLA), which play a role in the immune system by differentiating foreign substances and the body's substances (Rautiainen et al 2016). The *BTNL2* gene regulates T-cell multiplication in the immune system ("BTNL2"). It was unclear how the alteration of these genes affected cognitive mechanisms since these genes are only known to play a role in the immune system.

Furthermore, ASPD has the potential to be genetically transmitted to offspring, because the mutations may pass onto the offspring from the parent (Rautiainen et al 2016). A potential limitation could be the insufficient number of subjects involved — there were only 370 cases and 5850 controls (Rautiainen et al 2016). There were so few females that they were unable to find statistically significant SNPs in females only, while they were able to find strong results in males only and both sexes (Rautiainen et al 2016). The following GWAS study by Barr et al. has a much larger sample size of 15,112, while Rautiainen et al. only has 6,220 participants (Rautiainen et al 2016) (Barr et al 2020). Interestingly, Barr et al. believed that even 15,112 was not enough for accurate results — a sample size in the hundreds-thousands would finally be sufficient (Barr et al 2020). If 15,112 was considered inadequate for accurate results, then 6,220 was not either. Future GWAS research should aim to have a much larger sample size to increase statistical power.

The second GWAS by Barr et al. was conducted on families with European ancestry (EA) and African ancestry (AA) (Barr et al 2020). As previously mentioned, they used a sample size of 15,112, which was still considered "underpowered" (Barr et al 2020). Barr et al. discovered 3 SNPs that were commonly found in both EA and AA families, except one of them (i.e. rs2376620) was found predominantly in EA than AA families (Barr et al 2020). At the first glance, some may believe that this is because EA and AA families are genetically different (Barr et al 2020). However, many in the science community believe that there is more genetic variation within a race than between races, meaning that different races are not extremely different genetically. Then, why is there a difference between Caucasian and African American families when it comes to the significance of the SNP's relationship to ASPD? Although there may be less genetic variation between races than within races, it does not mean there is a total absence of variation between the races. Thus, it would be okay to add racial diversity to the

sample size for a good measure of including all the possible variations. Additionally, the sample size of EA families is nearly twice as large as AA families, thus, a SNP might appear more often in the larger sample (Barr et al 2020). The remaining two SNPs discovered by this GWAS were found in both EA and AA families (Barr et al 2020).

In total, these 3 genome-wide significant SNPs — rs2376620, rs2433198, and rs12928255 — may increase the risk of developing externalizing behaviors, including ASPD (Barr et al 2020). Rs2376620 was on the *CDKN1A* gene, which creates a protein that responds to stress stimuli (Barr et al 2020). This variant may disrupt one's ability to respond to stress and lead to antisocial or externalizing behavior ("CDKN1A"). Rs2433198 was in the locus: *GCOM1/MYZAP*, which codes proteins that allow transcription of other genes, but it does not appear to affect any other mechanisms (Barr et al 2020) ("GCOM1"). Thus, modifications of this locus may lead to transcription errors in other genes that are relevant to externalizing disorders. Finally, rs12928255 was found in the *PKD1L2* gene, which is a pseudogene that's unable to code proteins ("PKD1L2") ("Pseudogene") (Barr et al 2020). A possible explanation for its relationship with ASPD is that the mRNA of the *PKD1L2* gene could be active, although it does not create a protein. It could also regulate the transcription of other genes that directly affect externalizing disorders. This indicates an unclear understanding of how *PKD1L2* impacts mechanisms leading to ASPD. Therefore, these 3 genome-wide significant SNPs found in EA and AA families — rs2376620, rs2433198, and rs12928255 — may lead to externalizing behaviors, including ASPD (Barr et al 2020).

As mentioned before, a limitation was that their results are not robust enough to replicate and confirm their findings, meaning that these variants may not be completely accurate due to insufficient sample size (Barr et al 2020). Therefore, this study could have improved the accuracy of its results by upgrading its sample size so it could replicate and confirm some variants. Next, their identified SNPs contribute to externalizing disorders in general — this could include ASPD and other disorders such as alcohol abuse and drug abuse (Barr et al 2020). Thus, these findings are not specific to ASPD, but to the general category of externalizing disorders. Overall, possessing one of the 3 mentioned SNPs increases the risk of developing externalizing behaviors like ASPD in families of European and African ancestry (Barr et al 2020).

The next study by DeLisi et al. investigates how childhood adversity and psychopathology — other mental illnesses — correlate with ASPD symptoms and official diagnosis in adulthood (DeLisi et al 2019). The participants were compared to each other by their ASPD status — whether they had symptoms only, were officially diagnosed, or had no evidence of ASPD (DeLisi et al 2019). Possible reasons could be to determine key variables that cause mostly symptoms, mostly diagnosis, both, or neither. Results showed that physical abuse was the type of adverse experience with the strongest correlation with ASPD symptoms, which was closely followed by sexual abuse (DeLisi et al 2019). Physical abuse may be the leading cause of symptoms because these experiences lead to hostility, scorn, skepticism of adult authority, irritability, aggression, and disregard towards others (DeLisi et al 2019). A mental illness that may have played a role in ASPD symptoms was conduct disorder because it possesses the strongest relationship and possesses the same symptoms as ASPD, but in minors only (DeLisi et al 2019) (Rockville et al 2016). Finally, another aspect that could lead to symptoms was arrest onset during adolescence or childhood, which was not as strongly correlated as the mentioned variables but still somewhat predicted ASPD symptoms (DeLisi et al 2019). In contrast, sexual abuse was the leading predictor of official ASPD diagnosis, possibly

because the severity of the experiences may lead to the worst issues with adaptation and adjustments (DeLisi et al 2019). Another closely following adverse childhood experience was physical abuse (DeLisi et al 2019). Once again, CD was proven to be a remarkable predictor of ASPD diagnosis with its soaring Relative Risk Ratio of 11.28 (DeLisi et al 2019). Although this seems like a statistical outlier, this result could be due to the degree of overlap between the symptoms of CD and ASPD — the main difference between them is that CD is a diagnosis for minors only (Rockville et al 2016). Abuse may have high correlations with ASPD symptoms and diagnosis because these experiences could be so adverse that it permanently affects their behavior epigenetically. Additionally, having conduct disorder and arrests during childhood could be strong predictors of developing ASPD in the future because the disorders are similar in symptoms.

However, there was a lack of balance in the races and sexes — the sample was 84% male, 16% female, 79.4% Caucasian, and 20.6% African American (DeLisi et al 2019). As shown, there was a disproportionate division between males and females, which was a problem because results for females could be different (DeLisi et al 2019). This issue also appeared in several other studies (Rautiainen et al 2016) (Kumari et al 2012) (Glenn et al 2013). Additionally, this study only consists of Caucasians and African Americans (with Caucasians dominating), making conclusions about other races unclear (DeLisi et al 2019). Thus, creating an equilibrium and increasing the variety of races should be considered for future studies. Some may wonder why race matters so much if there was more genetic variation within a race than between races, which is a commonly accepted theory in the scientific community. However, environmental differences may lead to different behavioral outcomes — in the United States, there is a significant difference between the typical Caucasian family's environment and African American family's environment (Patnaik et al 2020). For instance, there are significant economic wage gaps, African Americans are 75% more likely than White people to live in fence-line communities (zones near commercial facilities that cause noise, traffic, odor, and chemical emissions), and lower socioeconomic statuses, health statuses, and income levels are more prevalent in African American communities due to systemic racism (Patnaik et al 2020). Such differences between the environments may impact whether certain groups have behavioral variation. Therefore, it's necessary to include a variety of races in this study — not because of the different racial ancestries being naturally different by genetics, but because of environmental factors that could affect the risk of developing ASPD.

The next review on ASPD touches on its environmental etiology (Glenn et al 2013). A significant finding from one of the mentioned articles was that people with ASPD have spent increased time watching television during their childhood and adolescence (Glenn et al 2013). A theorized explanation behind this was that the observational learning theory took place, which involves the imitation of actions seen on the TV, causing callousness, a normalized attitude towards brutality, aggression, and deprivation of social interaction (Glenn et al 2013). However, they do not know for sure whether their participants were watching violent content or not, making them uncertain that watching violent content caused the observational learning theory and ASPD (Glenn et al 2013). Another large environmental factor was the level of psychosocial deprivation (Glenn et al 2013). For instance, the quality of maternal care during people's early lives mattered a lot — if a mother neglects or abuses an infant or child, psychosocial deprivation will alter the brain structure — especially the prefrontal cortex and inferior frontal region — which is a predictor and potential cause of ASPD (Glenn et al 2013). The researchers recognized that psychosocial deprivation, such as neglect and abuse, decreased the prefrontal cortex and

inferior frontal region of the brain in subjects with ASPD and without, while a decrease in the thalamus occurred in ASPD subjects only (which filters sensory information) (Kumari et al 2012) (Glenn et al 2013). Consequently, a smaller prefrontal cortex and inferior frontal region lead to trouble with behavioral control, inhibition (self-consciousness), and the ability to make reasonable decisions, while a deficit in the thalamus volume induces difficulty in extinguishing intrusive thought and memories related to preceding mistreatment (Kumari et al 2012) (Glenn et al 2013). Although psychosocial deprivation did not have a strong correlation with ASPD (since both violent and non-violent subjects could have it), it could lead to a decrease in the prefrontal cortex, inferior frontal region, and thalamus, increasing the risk of ASPD symptoms (Kumari et al 2012) (Glenn et al 2013). In addition to maternal neglect, watching the television was also an action that lacks social activity, so it may trigger psychosocial deprivation and adapt the brain's functions into expressing antisocial behavior (Glenn et al 2013). However, Kumari et al.'s sample only consisted of 56 males, which is somewhat insubstantial and not diverse based on sex (Kumari et al 2012). Overall, television and psychosocial deprivation levels were significant environmental factors that increased the chance of antisocial personality (Glenn et al 2013).

The following two articles — by Philibert et al. and Checknita et al. — focused on the correlation between methylation at the *MAOA* gene and antisocial behavior. Philibert et al. discovered that ASPD phenotypes are derived from the epigenome at *MAOA* P1 and P2 VNTRs (Philibert et al 2011). Experimental results showed that the 10R genotype of the P2 region was the most methylated, disrupted binding sites for transcription, lowered enhancement and gene expression, downregulated monoaminergic neurotransmitter levels, and increased the risk of antisocial personality (Philibert et al 2011). To note, these results mostly apply to middle-aged White subjects only because the sample was primarily White and in their late 40s (Philibert et al 2011). This indicates the lack of diversity in the sample, which was something future scientists should avoid in genotyping. Expanding the racial and age diversity of this sample may have contributed to findings of different DNA sequences, methylated alleles, and conclusions (Philibert et al 2011). Critics may argue that the majority of the scientific community believes that there is more genetic variation within a race than between races, thus, race should not matter too much in this study. As mentioned before, the typical Caucasian family's environment and African American family's environment may be very different and lead to epigenetic variation (Patnaik et al 2020). There are significant economic wage gaps, African Americans are 75% more likely than White people to live in fence-line communities, and lower socioeconomic statuses, health statuses, and income levels are more prevalent in African American communities (Patnaik et al 2020). Different environmental stimuli may trigger methylation and lead to different gene expression patterns and a different epigenome, thus, it's crucial to include a variety of races in this study. Due to the lack of diversity in the sample, Philibert et al.'s results apply mostly to middle-aged Caucasians (Philibert et al 2011).

Checknita et al. did not clarify their sample's racial distribution, but they studied *MAOA* and identified a Region of Interest that was extremely methylated (Checknita et al 2015). After investigating how it impacted gene expression, they realized that hypermethylation in this ROI led to the blockage of transcription factors and prohibited gene expression (Checknita et al 2015). The MAOA enzyme contributed to regulating serotonin levels and aggression, thus, the deficiency of MAOA may lead to a deficiency of serotonin (5-HT), which was discussed in the final article about epigenetics (Checknita et al 2015) (Beach et al 2010). This study's luciferase assessments indicated that methylation in the ROI substantially prohibited gene expression and MAOA enzyme activity, while unmethylation in the same locus upregulated MAOA levels. Thus,

the methylation levels in the identified Region of Interest (678 bp) had a significant impact on MAOA levels and behavior characteristics of ASPD (Checknita et al 2015). In addition to hypermethylation decreasing MAOA enzymatic production, it also caused abnormal serotonin levels (Checknita et al 2015). Interestingly, Checknita et al. theorized that there would only be a deficiency of 5-HT (serotonin) in the central nervous system, but to manage an equilibrium, there will be an unexpected increase in 5-HT levels in the blood, leading to increased aggression (Comai et al 2012) (Moffitt et al 1998) (Checknita et al 2015). Therefore, this study's findings indicate that hypermethylation of the *MAOA* gene leads to decreased MAOA enzymatic production, decreased serotonin levels in the central nervous system, and contrarily, increased serotonin levels in the blood of individuals with ASPD (Checknita et al 2015). However, the theory on 5-HT levels is flawed, which will be elaborated on next.

One limitation is that the sample was extremely limited — there were only 86 cases and 74 controls, totaling 160 subjects overall (Checknita et al 2015). Compared to the previous study, Philibert et al.'s sample was 3.57 times larger than Checknita et al.'s, indicating that this study was much less powerful (Checknita et al 2015) (Philibert et al 2011). Subsequently, the results may not be accurate due to using blood in substitution for extracting brain tissue, but this could not have been avoided since the participants were living (Checknita et al 2015). Furthermore, there was no confirmation for the theory of blood 5-HT levels in the case being higher than the healthy cohort, because this experiment never assessed the control's 5-HT levels (Checknita et al 2015). Since Checknita et al. theorized 5-HT levels being higher in the blood of people with ASPD based on other papers, this flaw indicates that their theory was not supported by their results. The upcoming, final article on epigenetics in ASPD investigates the methylation of the *5HTT* gene (Beach et al 2010). Lastly, this study does not have a clear answer about whether *MAOA* methylation was directly associated with ASPD or mediated by environmental experiences, such as childhood adversity (Checknita et al 2015). Beach et al. confirmed that methylation of a similar gene mediates environmental adversities and the development of ASPD by investigating serotonin levels among women with ASPD (Beach et al 2010).

Methylation of the *5HTT* allele modifies serotonin levels, which impacts mood, sensory processing, cognition, and sleep (Beach et al 2010). Alterations in the levels of this neurotransmitter may lead to numerous behavioral problems, including ASPD (Beach et al 2010). However, people with the L allele may not always respond this way to the methylation of *5HTT*, while people carrying an S allele at *5HTT* may respond by showing behavioral traits from ASPD (Beach et al 2010). Cornelius et al. explained that individuals with an S allele are 2-2.5 times more likely to downregulate serotonin transcription compared to an L allele, heightening the risk of several personality disorders (Cornelius et al 2014). In addition to discovering that alleles moderate behavioral responses to methylation, Beach et al. noted that women who have experienced childhood sexual abuse often had methylation at *5HTT* (Beach et al 2010). This could be due to the severe stress that comes along with sexual abuse, which signals to methylate the gene (Beach et al 2010). However, sexual abuse did not directly correlate with ASPD because methylation of *5HTT* may also lead to disorders other than ASPD, such as major depressive disorder and alcohol dependence (Beach et al 2010). Thus, the relationship between sexual abuse and ASPD was weak, but the relationship between sexual abuse and methylation of *5HTT* was strong, along with *5HTT* methylation and ASPD (Beach et al 2010). Therefore, the epigenome of *5HTT* mediates the association between sexual abuse in women and antisocial personality disorder (Beach et al 2010).

Antisocial personality disorder does not have a single cause. Having certain genetic variations can transmit the disorder to offspring genetically, according to GWAS (Rautiainen et al 2016) (Barr et al 2020). Environmental factors, such as childhood adversity (i.e., neglect, physical and sexual abuse) and comorbid psychopathological circumstances (i.e., CD, arrest onset) are significant causes and predictors, respectively, of the disorder (DeLisi et al 2019). Certain lifestyles and exposure to violence during childhood may also impact one's chances of developing ASPD (Glenn et al 2013). On a deeper level, the environment may even impact gene expression by adding methyl tags to the epigenetic profile (Philibert et al 2011) (Checknita et al 2015) (Beach et al 2010). Methylation of certain genes downregulates their expression and alters certain cognitive mechanisms, eventually leading to the development of disorders such as ASPD (Philibert et al 2011) (Checknita et al 2015) (Beach et al 2010). Even by investigating the complex etiology of this disorder, there is currently no effective treatment for ASPD ("Causes, Symptoms" 2021). In individuals who've genetically inherited an SNP that may lead to ASPD, an option to moderate antisocial behaviors is medication or psychotherapy in minors diagnosed with conduct disorder and other significant predictors of ASPD ("Causes, Symptoms" 2021). Limiting television viewing, exposure to violence, neglect, abuse, mistreatment, and adverse experiences in children and adolescents may prevent the development of the disorder due to environmental factors. Demolishing environmental risks as much as possible may prevent the epigenome from downregulating the expression of certain genes, inducing alterations in cognition, causing ASPD, and passing it on to future generations. Future studies should focus on having diverse samples based on race, age, and sex for more accurate results. Further research may or may not verify this theory of preventing ASPD based on reviewing its genetic, environmental, and epigenetic etiology.

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Abbreviations

AA	African ancestry
ASPD	Antisocial personality disorder
CD	Conduct disorder
EA	European ancestry
GWAS	Genome-wide association study
IAS	Iowa Adoption Studies
MAOA	Monoamine Oxidase A
RRR	Relative risk ratio

References

1. “Antisocial Personality Disorder: Causes, Symptoms & Treatment.” *Cleveland Clinic*, 12 May 2021, https://my.clevelandclinic.org/health/diseases/9657-antisocial-personality-disorder.

2. Barr, Peter B., et al. “A Family-Based Genome Wide Association Study of Externalizing Behaviors.” *Behavior Genetics*, vol. 50, no. 3, 2020, pp. 175–183., https://doi.org/10.1007/s10519-020-09999-3.

3. Beach, Steven R., et al. “Methylation at 5HTT Mediates the Impact of Child Sex Abuse on Women's Antisocial Behavior: An Examination of the Iowa Adoptee Sample.” *Psychosomatic Medicine*, vol. 73, no. 1, 14 Oct. 2010, pp. 83–87., https://doi.org/10.1097/psy.0b013e3181fdd074. Accessed 24 Nov. 2022.

4. “BTNL2 Butyrophilin like 2 [Homo Sapiens (Human)] - Gene - NCBI.” *National Center for Biotechnology Information*, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene/56244.

5. “CDKN1A Cyclin Dependent Kinase Inhibitor 1A [Homo Sapiens (Human)] - Gene - NCBI.” *National Center for Biotechnology Information*, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene?Cmd=DetailsSearch&Term=1026.

6. Checknita, D., et al. “Monoamine Oxidase a Gene Promoter Methylation and Transcriptional Downregulation in an Offender Population with Antisocial Personality Disorder.” *British Journal of Psychiatry*, vol. 206, no. 3, Mar. 2015, pp. 216–222., https://doi.org/10.1192/bjp.bp.114.144964.

7. Comai, Stefano, et al. “The Psychopharmacology of Aggressive Behavior.” *Journal of Clinical Psychopharmacology*, vol. 32, no. 1, Feb. 2012, pp. 83–94., https://doi.org/10.1097/jcp.0b013e31823f8770.

8. Cornelius, Jack R, et al. “The ‘S’ Allele of the Serotonin Transporter Is Not Associated with Major Depression or Alcohol Use Disorders in a Veteran Sample.” *International Journal of Medical and Biological Frontiers*, U.S. National Library of Medicine, 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504693/.

9. DeLisi, Matt, et al. “The Etiology of Antisocial Personality Disorder: The Differential Roles of Adverse Childhood Experiences and Childhood Psychopathology.” *Comprehensive Psychiatry*, vol. 92, 2019, pp. 1–6., https://doi.org/10.1016/j.comppsych.2019.04.001.

10. “DSM-IV and DSM-5 Criteria for the Personality Disorders.” American Psychiatric Association, 2012.

11. “Epigenetics & Inheritance.” *Learn Genetics*, https://learn.genetics.utah.edu/content/epigenetics/inheritance/.

12. “Epstein-Barr and Infectious Mononucleosis (MONO).” *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 28 Sept. 2020, https://www.cdc.gov/epstein-barr/index.html.

13. Ferguson, Christopher J. “Genetic Contributions to Antisocial Personality and Behavior: A Meta-Analytic Review from an Evolutionary Perspective.” *The Journal of Social Psychology*, vol. 150, no. 2, 2010, pp. 160–180., https://doi.org/10.1080/00224540903366503.

14. “GCOM1 GCOM1, MYZAP-POLR2M Combined Locus [Homo Sapiens (Human)] - Gene - NCBI.” *National Center for Biotechnology Information*, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene/145781#summary.

15. “Gene Control.” *Learn Genetics*, https://learn.genetics.utah.edu/content/epigenetics/control/.

16. “Genomic Imprinting.” *Learn Genetics*, https://learn.genetics.utah.edu/content/epigenetics/imprinting/.

17. Glenn, Andrea L., et al. “Antisocial Personality Disorder: A Current Review.” *Current Psychiatry Reports*, vol. 15, no. 12, 2013, https://doi.org/10.1007/s11920-013-0427-7.

18. Guilherme, L., et al. “Rheumatic Heart Disease.” *Advances in Clinical Chemistry*, 2011, pp. 31–50., https://doi.org/10.1016/b978-0-12-385855-9.00002-3.

19. Iyegbe, Conrad O., and Paul F. O’Reilly. “Genetic Origins of Schizophrenia Find Common Ground.” *Nature*, vol. 604, no. 7906, 2022, 11 Apr. 2022, pp. 433–435., https://doi.org/10.1038/d41586-022-00773-5.

20. Kellis, Manolis et al.Massachusetts Institute of Technology via MIT OpenCourseWare, et al. “Book: Computational Biology - Genomes, Networks, and Evolution (Kellis Et Al..).” *Biology LibreTexts*, 3 Jan. 2021, https://bio.libretexts.org/Bookshelves/Computational_Biology/Book%3A_Computational_Biology_-_Genomes_Networks_and_Evolution_(Kellis_et_al.).

21. Kroemer, Tyasning. “A Deep Dive into the Luciferase Assay: What It Is, How It Works and More.” *GoldBio*, https://goldbio.com/articles/article/a-deep-dive-into-the-luciferase-assay-what-it-is-how-it-works-and-more.

22. Kumari, V., et al. “Reduced Thalamic Volume in Men with Antisocial Personality Disorder or Schizophrenia and a History of Serious Violence and Childhood Abuse.” *European Psychiatry*, vol. 28, no. 4, 2012, pp. 225–234., https://doi.org/10.1016/j.eurpsy.2012.03.002.

23. Mayo Clinic Staff. “Antisocial Personality Disorder.” *Mayo Clinic*, Mayo Foundation for Medical Education and Research, 10 Dec. 2019,

https://www.mayoclinic.org/diseases-conditions/antisocial-personality-disorder/symptoms-causes/syc-20353928.

24. Moffitt, Terrie E., et al. “Whole Blood Serotonin Relates to Violence in an Epidemiological Study.” *Biological Psychiatry*, vol. 43, no. 6, 1998, pp. 446–457., https://doi.org/10.1016/s0006-3223(97)00340-5.

25. Moore, Derick. “U.S. Population Estimated at 332,403,650 on Jan. 1, 2022.” *Census.gov*, 13 Apr. 2022, https://www.census.gov/library/stories/2021/12/happy-new-year-2022.html.

26. Nica, Alexandra C., and Emmanouil T. Dermitzakis. “Expression Quantitative Trait Loci: Present and Future.” *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 368, no. 1620, 2013, p. 20120362., https://doi.org/10.1098/rstb.2012.0362.

27. Patnaik, Aneesh, et al. “Racial Disparities and Climate Change - Psci.” *Princeton University*, The Trustees of Princeton University, 15 Aug. 2020, https://psci.princeton.edu/tips/2020/8/15/racial-disparities-and-climate-change.

28. Philibert, Robert A., et al. “Gene Environment Interactions with a Novel Variable Monoamine Oxidase a Transcriptional Enhancer Are Associated with Antisocial Personality Disorder.” *Biological Psychology*, vol. 87, no. 3, 2011, pp. 366–371., https://doi.org/10.1016/j.biopsycho.2011.04.007.

29. “PKD1L2 Polycystin 1 like 2 (Gene/Pseudogene) [Homo Sapiens (Human)] - Gene - NCBI.” *National Center for Biotechnology Information*, U.S. National Library of Medicine, https://www.ncbi.nlm.nih.gov/gene/114780.

30. “Promoter.” *National Human Genome Research Institute Home | NHGRI*, 10 May 2022, https://www.genome.gov/genetics-glossary/Promoter.

31. “Pseudogene.” *Genome.gov*, https://www.genome.gov/genetics-glossary/Pseudogene.

32. Raine, Adrian, et al. “Reduced Prefrontal Gray Matter Volume and Reduced Autonomic Activity in Antisocial Personality Disorder.” *Archives of General Psychiatry*, vol. 57, no. 2, 2000, p. 119., https://doi.org/10.1001/archpsyc.57.2.119.

33. Rautiainen, M-R, et al. “Genome-Wide Association Study of Antisocial Personality Disorder.” *Translational Psychiatry*, vol. 6, no. 9, 6 Sept. 2016, https://doi.org/10.1038/tp.2016.155.

34. Reddy, Umesh K., et al. “Genome-Wide Divergence, Haplotype Distribution and Population Demographic Histories for Gossypium Hirsutum and Gossypium Barbadense as Revealed by Genome-Anchored Snps.” *Scientific Reports*, vol. 7, no. 1, 2017, https://doi.org/10.1038/srep41285.

35. Robertson, Lindsay A., et al. “Childhood and Adolescent Television Viewing and Antisocial Behavior in Early Adulthood.” *Pediatrics*, vol. 131, no. 3, 2013, pp. 439–446., https://doi.org/10.1542/peds.2012-1582.

36. Rockville, Heather Ringeisen, et al. “DSM-5 Changes: Implications for Child Serious Emotional Disturbance [Internet].” *National Center for Biotechnology Information*, U.S. National Library of Medicine, June 2016, https://pubmed.ncbi.nlm.nih.gov/30199184/.

37. Shi, Zhenyu, et al. “Childhood Maltreatment and Prospectively Observed Quality of Early Care as Predictors of Antisocial Personality Disorder Features.” *Infant Mental Health Journal*, vol. 33, no. 1, 2012, pp. 55–69., https://doi.org/10.1002/imhj.20295.

38. Shlyueva, Daria, et al. “Transcriptional Enhancers: From Properties to Genome-Wide Predictions.” *Nature Reviews Genetics*, vol. 15, no. 4, 2014, pp. 272–286., https://doi.org/10.1038/nrg3682.

39. “The Epigenome at a Glance.” *Learn Genetics*, https://learn.genetics.utah.edu/content/epigenetics/intro/.

40. “The Epigenome Learns from Its Experiences.” *Learn Genetics*, https://learn.genetics.utah.edu/content/epigenetics/memory/.

41. Vaughn, Michael G., et al. “The Antisocial Family Tree: Family Histories of Behavior Problems in Antisocial Personality in the United States.” *Social Psychiatry and Psychiatric Epidemiology*, vol. 50, no. 5, 2014, pp. 821–831., https://doi.org/10.1007/s00127-014-0987-9.

42. Werner, Kimberly B., et al. “Epidemiology, Comorbidity, and Behavioral Genetics of Antisocial Personality Disorder and Psychopathy.” *Psychiatric Annals*, vol. 45, no. 4, 1 Apr. 2015, pp. 195–199., https://doi.org/10.3928/00485713-20150401-08.

43. “Z-Score Introduction (Video) | Z-Scores.” *Khan Academy*, Khan Academy, https://www.khanacademy.org/math/ap-statistics/density-curves-normal-distribution-ap/measuring-position/v/z-score-introduction.