From a genetic predisposition till actual aggressive and antisocial behavior

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Aggressive and antisocial behavior in most extreme forms acclaimed political and media awareness since the 1960s due to an abnormal rise in psychopathic killing sprees. This placed particular focus in research on the etiology of this kind of behavior (Pieri and Levitt 2008). Individuals with an antisocial personality show a pattern of aggression, impulsivity and deceitfulness and always violate or disregard rights of others. Antisocial behavior usually emerges in childhood or early adolescence and often continues into adulthood (Glenn et al., 2013). It is classified by the Diagnostic and Statistical Manual (DSM) as a developmental disorder more common in males and approximately 2% of the population develops it. Antisocial behavior is also often associated with psychopathic traits. These traits have a callous-unemotional and an impulsive-antisocial component (Blair 2013). Individuals with an antisocial personality disorder almost always display low self-control, which is a major underlying aspect that determines behavior. Self-control is a broad term that covers a wide range of characteristics that are shaped during childhood by empirical observation (Moffitt et al., 2011). Children that are unable to acquire sufficient self-control tend to accelerate in antisocial trait behavior. Self-control influences many factors like social and financial welfare, friendship, success and health. The lack of self-control therefore negatively influences the quality of life and it is presumed to be the main cause of criminal behavior (Moffitt et al., 2011).

The development of antisocial behavior, and behavior in general, depends on genetic and environmental interplay. All individuals are emotionally, experientially, attitudinally, interpersonally and motivationally different (McCrae and John 2006). The etiology of antisocial behavior however, remains largely unknown. Therefore, the influence of genetics and the environment on acquiring self-control or antisocial personality traits has been studied immensely the last decades (Tuvblad and Baker 2011). Questions like; does...
one outweigh the other or do they contribute equally?: can a genetic propensity pronounce more emphasis in certain situations over others? (Tuvblad and Baker 2011) and are there specific pathways involved in aggression and antisocial traits?, have been dominating the scene. Scientist have also been focused on the identification of specific environmental factors and genetic variations that are risk factors for this kind of behavior. The last decade media has provided information that the so-called “warrior gene” and child abuse are important contributing factors. Most predominant environmental factors have indeed been identified as adverse childhood experiences and a few genetic variations have been identified that are involved in the modulation of endogenous brain chemicals like neurotransmitters (Yanowitch and Coccaro 2011).

The purpose of this review is to outline currently known genetic risk factors for antisocial behavior and provide these factors with examples of well-known individuals that have behaved in an actual aggressive and antisocial manner. First, a basic understanding of personality and behavior is provided and the complexity of genetic and environmental interplay is explained. Secondly, mostly genetic and some environmental factors that influence personality and behavior will be discussed and famous case reports will be outlined. Finally, this review discusses the implications of behavioral genetics today and their ramifications on society and legal proceedings. The important observation that the onset of aggressive and antisocial behavior, as well as behavior itself, is a complex of consecutive factors, where one influences the other and the outcome is therefore never set from the start, is further emphasized in this review.

Nature and nurture of behavior

The big five is a widespread model of personality that organizes personality traits into five basic dimensions: extraversion, neuroticism, conscientiousness, agreeableness and openness to experience. Extraversion is established based on traits like activeness, assertiveness, enthusiasm and neuroticism is based on objectives like anxiousness, tenseness, stability etc. Conscientiousness is based on reliability, organization skills, trustfulness etc. Agreeableness is based on how generous, forgiving or kind an individual is and openness to experiences is based on curiousness, creativity and other artistic characteristics (McCrae and John 2006). Acquiring self-control, a major underlying mechanism that determines social behavior, has traits that overlap with all five dimensions and those dimensions are all subjected to genetic and environmental influences.

A home environment strongly influences behavioral development. Most personality traits are not set but shaped during childhood and environmental influences are therefore prime during development. Age is known to be a reflection of biological maturation and the accumulation of experiences (Rutter 1989). Individuals still experience developmental changes into adulthood, however these changes are moderate and less radical. Certain environmental moderators that negatively influence development have already been identified. Adverse childhood experiences like child abuse is probably the most important factor that can contribute to the development of antisocial behavior (Douglas et al., 2010). Children that have been maltreated, emotionally neglected and physically abused are statistically proven to be more prone to aggressive and antisocial behavior. The occurrence of adverse effects emerging below the age of one has even been associated with most severe antisocial problems (Caspi et al., 2002), which also indicates the essence of timing.

Genetics determines physical appearances, but also a person’s well being and behavior. The genetic basis of behavior has not been studies as immensely as the environmental basis of behavior (Tuvblad and Baker 2011), because correlations between genetic factors and behavioral traits are more difficult to examine. This is due to the complexity of gene function in general. Not all genes are evenly correlated to phenotypic traits. One gene in particular is for instance able to influence multiple phenotypic traits and multiple genes are also able to influence one particular trait. Additive genetic effects occur when multiple genes individually encode for the same function and non-additive genetic effects occur due to epistatic interactions and dominance deviations (Bemmels et al., 2008). Therefore the classification of multiple genetic alleles, as well as the identification of individual alleles are important in uncovering the etiology of behavior.

There are three different types of environmental and genetic interplay. The first type is the genetic and environmental interaction. This emphasis how strong the interaction between genes and the environment can be during different life stages or situations. This type of interplay is strongly subjected to changes and these changes mediate a constant shift in interaction. Environmentally stressed can for instance push genetically vulnerable individuals towards a clinical disorder (Kendler and Baker 2007). The second type of interplay relates to genetic and environmental correlations (Scarr and McCartney 1983). The environment an individual resides in can reflect ones genetic traits. This is established by actively selecting or evoking experiences consistent with certain genetic traits that evokes others with complementary traits. Just as a certain personality associates with similar personalities, that sometimes evoke aberrant personalities. The third type of interplay relates to experience-based activation of epigenetic mechanisms that alters gene expression (Meaney 2010). The environment is known to indirectly alter the effects of genes by affecting gene expression through epigenetics. Environmental induced DNA damage is also known to change gene expression patterns through disruptions of the genomic sequence, which occurs at random. The environment, however, is never able to change gene expression patterns directly.
The distinction between heritability and environment is not always clear. In relation to life events, not all seemingly environmental experiences are entirely caused by environmental factors. Independent life events are events that occur at random and are therefore uncontrollable, however, dependent life event are more prone to individual choices and behavior and they can therefore have a large heritable component (Bemmel et al., 2008).

Environmental and genetic interplay is extremely complex and important in the development of behavior. According to neuroscientist James Fallon the timing of interplay that mediates adverse effects on behavior is very crucial in determining whether an individual does or does not develop antisocial traits. It also strongly depends of the developmental age of that individual at that moment.

**Methods of assessing gene-environment interactions**

What part of (antisocial) behavior that is determined by genetics, can be assessed by methods that are able to separate nature from nurture.

The most straightforward method is to investigate individuals from the same family where aggression and antisocial behavior is common. Two designs combined proved to be very powerful in separating heritability from the environment. This is based on classic studies of twins raised together and studies of adopted individuals and adoptive and biological family members (Tvublad and Baker 2011). These studies are effective but the occurrences of these types of relations with antisocial personality traits are rare. Most of these studies have indicated that heritability accounts for approximately 30-50% of human behavior. Interesting is that heritability increasingly defines human behavior with age and the environment increasingly defines behavior with age (Tvublad and Baker 2011; Bemmel et al., 2008). This is in line with the fact that children are more vulnerable to outside influences than adults and also because adolescences leave home to shape their own destinies. The contribution of genetics and the environment will always be an estimation because these studies display major inconsistencies due to discords in the definition of aggressive behavior and the methods of how it is measured and by who. Antisocial behavioral studies are often based on either criminal convictions, evidence of acts regardless of conviction, observational studies or self-report questionnaires (Pieri and Levitt 2008).

Although, single genes account for a small proportion of the overall genetic variance of behavior (Glenn et al., 2013), the identification of genes that pose as a risk factor helps to unravel the etiology of antisocial behavior. The last decades methods to assess these gene-environment interactions have been conducted from different starting points.

Some methods focus on identifying genetic variants that are common in individuals that display certain behavioral traits and are therefore conducted from a behavioral starting point. A widely used method to assess genetic susceptibilities to disorders is by applying a genome-wide association study (GWAS). This method is based on searching for common genetic variants in individuals with a particular trait from a large cohort of randomly selected individuals. The largest part of heritable variance in relation to antisocial behavior has not been uncovered by GWASs (Bentley et al., 2013). GWASs, however, did generate a list of polymorphisms that were associated with antisocial behavior (Blair 2013) and some of them were even identified as such. Another more straightforward strategy in search for common genetic variants is to only select individuals with an aggressive and antisocial personality. This is also optional for testing association between candidate genes in particular trait groups (Erbstein 2006). Besides association studies, also family based linkage studies have been very successful in identifying genes involved in antisocial behavior. The first susceptibility-gene has been discovered due to a suspicion raised because of an abnormal amount of male family members that displayed antisocial behavior (Brunner et al., 1993).

Other methods to assess gene-environment interactions conduct research from a behavioral and environmental starting point combined. These methods have proven to be very successful because they search for common genetic variants in individuals with an antisocial personality that also encountered adverse childhood experiences. The environment is known to define behavior predominantly in early childhood and several physiological studies have indicated that child abuse is one of the main risk factors for antisocial behavior (Douglas et al., 2010). An interaction of genetic and environmental risk factors is more likely to induce the onset of antisocial behavior in children, than a genetic or environmental risk factor alone. Research about the identification of genetic risk factors in general is therefore predominantly done in individuals that already experienced environmental risk factors at a young age.

**Identification of genetic predispositions to antisocial behavior**

**47.XYY karyotype**

The earliest identification of a genetic variations that is known to prone individuals towards aggressive and antisocial behavior involves the 47.XYY karyotype (Briken et al., 2006). Gotz et al. compared a large cohort of men containing the karyotypes XYY, XXY and control XY. They found that the group of males with a XYY karyotype had a higher prevalence of antisocial behavior and criminal convictions (Gotz et al., 1999). XYY males have higher levels of sex hormones, like testosterone, LH and FSH (Briken et al., 2006) and are more likely to develop psychosocial problems. Schroder et al. reported that among offenders, more sexual crimes occurred in XYY males (Schroder et al., 1981). A large part of the offenders, including the ones with a genetic susceptibility
experienced bad parenting while growing up. The frequency of antisocial behavior and aggression during stressful events was also found to be greater in 47,XXY boys compared to normal XY karyotype boys (Lalatta et al., 2012). This example reflects one of the most eminent forms of genetic alterations mediating antisocial behavior. It is currently thought that the Y-chromosome has 78 functional genes (Eme 2005). Seventy-eight genes represented in duplicate accounts for a major genetic deviation and this is probably the reason why the XYY karyotype strongly correlates with more extreme forms of antisocial behavior (BOX 1).

BOX 1: 47,XXY psychopathy and sexual homicides

Karyograms of a large cohort of sexual homicide perpetrators indicated that 23% had a XYY karyotype. Three of them, outlined here, were diagnosed as sexual sadists, showed psychopathic traits and had normal intelligence. They experienced learning difficulties and were physically abused during childhood. They began to display violent sexual behavior towards woman early in puberty. Sexual violence accelerated quickly and all men displayed serious sexual offences at age 15 and committed sexual homicides before the age of 20. They displayed forms of fetishes, narcissism and were all diagnosed with an antisocial personality disorder. All three men were incarcerated at a maximum age of 21 years old. They are fulfilling a long-term sentence. (Briken et al., 2006)

Interesting is that males are more prone to behave in an aggressive manor than females (Moffitt et al., 2001). Studies have indicated that the underlying etiology but also the environmental influences leading to antisocial behavior do appear to be very similar (Tuvblad and Baker 2011). Research has not indicated that males with a XXY karyotype are more prone to become antisocial than control XY males. Multiple duplications of X-chromosomes also do not appear to correlate to behavior in these extreme forms. This indicates that differences in antisocial behavior in relation to sex chromosome aneuploidies are Y-chromosome limited.

MAOA

Serotonin, dopamine and (nor)epinephrine are suggested to be associated with personality traits organized in dimensions like neuroticism, extraversion and openness to experiences (Ehstebin 2006). Neurotransmitters execute basis behavioral components and modulation effects are known to influence the vulnerability for aggressive behavior (Yanowitch en Coccaro 2011). Caspi et al. conducted research on a genetic polymorphism in the promoter region of the monoamine oxidase A gene (MAOA) in a cohort of boys that experienced maltreated (Caspi et al., 2002). This gene is in the media well known as the so-called “warrior gene”. The MAOA gene is located on chromosome X and encodes for an enzyme that converts neurotransmitters serotonin, dopamine, norepinephrine and epinephrine to metabolite intermediates. This particular polymorphism in the MAOA gene sequence encompass a 30bp sequence repeat present in 2-6 copies. Copies 2 and 3 are classified as high activity alleles and copies 3.5 and 4 as low activity alleles. Research conducted in 1993 already indicated that a MAOA null allele was linked with male antisocial behavior (Brunner et al., 1993) (BOX 2).

BOX 2: Extreme behavior in males of a Dutch family dating from 1870

In 1978, a woman sought help at the University hospital in Nijmegen. Almost all the males in her family showed erratic behavior, including her son, and she didn’t believed it to be a coincidence. One family member had forced his sisters to strip at knifepoint, another tried to run down his boss. One even tried to rape his own sister and this family violence appeared to had a long history dating from 1870. At first, all that scientist Brunner and colleagues could tell her was that the men in her family experienced X-linked mental retardation. A few decades later, due to gene-mapping techniques, Brunner et al. were able to find a marker located on the short arm of the X-chromosome that all violent men had and that some females were carrier of. One gene, located in the vicinity of the marker, was most likely to be the cause. This gene encoded for the enzyme MAOA, which breaks down certain neurotransmitters involved in the fight or flight response (norepinephrine), regulating mood (serotonin) and alertness (dopamine). As predicted, all violent men appeared to have a null allele for MAOA. Predicted effects in women with the same marker, were nullified by an intact MAOA gene located on the other X-chromosome (Brunner et al., 1993; “A Violence in the blood”, Discover Magazine, From the October 1993 issue).

This was the first publication of a gene that was associated with antisocial behavior (Lofrige et al., 2014). Caspi et al. showed that males with a low MAOA activity who experienced childhood maltreatment had a higher association with antisocial behavior than males with a high MAOA activity who experienced maltreatment. Eighty-five percent of a group of boys with low MAOA activity that experiences childhood maltreatment displayed some form of antisocial behavior (Caspi et al., 2002).

COMT

COMT has been associated with the neuroticism dimension of personality and traits like impulsivity,
reward and novelty seeking. COMT, like MAOA, is an enzyme involved in the catecholamine synthesis pathway. COMT converts the neurotransmitters dopamine, norepinephrine and epinephrine to metabolite intermediates. However, unlike MAOA, it is not enzymatically involved in the serotonergic system. A single base polymorphism (G/A) in a functional amino acid of the COMT genetic sequence, located on chromosome 22, mediates a amino acid shift of valine to methionine. Individuals that display this shift have a reduced COMT enzyme activity (Chen et al., 2004). This low activity allele has been associated with aggressive behavior and especially males that have two low activity alleles are at risk for developing violent tempers (Stein et al., 2005; Lofrida et al., 2014).

SLC6A4
Also genes that modulate neurotransmitters in the brain individually have been associated with antisocial behavior. The serotonergic system has been associated with traits of the neuroticism dimension of behavior like aggression and impulsivity (Ebstein 2006). The serotonin transporter (5-HTT) is responsible for the re-uptake of serotonin from the synaptic cleft. An indel polymorphism in the promoter region of the SLC6A4 gene, located on chromosome 17, that encodes 5-HTT is identified as a risk factor for psychopathological traits (Douglas et al., 2011). The tandem repeat polymorphism (5-HTTLPR) contains either a long repeat allele or short repeat allele and individuals that are heterozygote or homozygote for the short allele have significant reduced transcription of 5-HTT (Ebstein 2006). Several research papers indicated that individuals exhibiting a short allele are more susceptible to negative environmental factors (Lofrida et al., 2014; Sadeh et al., 2010). Other papers also found a correlation between individuals with the long allele and social problems (Sadeh et al., 2010). Different scientific studies together indicate that both alleles have been identified as risk factors for social problems and antisocial personalities, probably under different environmental circumstances (Douglas et al., 2011).

DRD4
The dopamine receptor family has also been associated with antisocial behavior. The dopaminergic system has been associated with traits of the extraversion dimension of behavior, like novelty and reward seeking. The dopamine D4 receptor (DRD4) is a gene located on chromosome 11 and displays a repeat polymorphism of 48 bps that varies from 1 till 11 copies. Copy numbers 1-5 are classified as short alleles and 6-8 as long alleles. The short alleles are known to lower gene expression and function (Lofrida et al., 2014). The DRD4 gene, like other genes involved in the dopaminergic pathway, has been linked to motivation responses, attention process regulation and exploratory behavior (Beaver et al., 2014). DRD4 is mostly brought to expression in the limbic system of the brain that mediates cognition and emotion and an underactive limbic system is known to be an indicator for psychopathic traits (Blair 2013). Several studies have indicated that adverse childhood experiences in combination with the short allele is highly associated with antisocial behavior, especially in young infants (Propper et al., 2007; Lofrida et al., 2014) Beaver et al. also investigated the gene × gene interaction of DRD4 and DRD2 and showed that the interaction of these two genes was more strongly correlated to antisocial behavior than each gene separately. The correlation between antisocial behavior and DRD2 has not been as widely demonstrated as the correlation with DRD4.

BOX 3: Abdelmalek Bayout- convicted citizen who got a lighter sentence due to a genetic predisposition

Bayout, an Algerian citizen living in Italy, stabbed and killed a man in 2007 for insulting him on wearing eye make-up. Bayout, wore his make-up for religious reasons, so he claims. Genetic tests indicated that Bayout had the genetic variations in the MAOA, COMT, DRD4 and SLC6A4 genes that were liked to violent and aggressive behavior. His lawyer argued that due to the combination of an abusive environment and a genetic disposition, Bayout was prone to become more aggressive under certain conditions. The judge stated that he lightened Bayout’s sentence based on this compelling evidence. His verdict has raised a worldwide discussion amongst scientists, psychologists and law enforcement officers that is still ongoing today. Nature | doi:10.1038/news.2009.1050 | Published online on the 30th of October, 2009.

Conclusion

The genetic polymorphisms that are outlined in this review are related to genes involved in the serotonergic, dopaminergic and adrenergic systems. These genes either have a single base polymorphism or a sequence repeat with a ranging copy number. Results from these four genetic polymorphisms indicate that high or remaining levels of neurotransmitters in the brain can have adverse behavioral repercussions when individuals experience adverse childhood effects during the developmental stage. These four genes do not affect behavior directly, only indirectly in the context of gene-environment interactions (Caspi et al., 2002; Pieri and Levitt 2008). Research indicates that the younger the infant, the more likely the child will develop social and psychological problems (Caspi et al., 2001).

There is thus a consensus in the literature that an individual has a higher risk of developing antisocial behavior whenever a genetic susceptibility towards antisocial behavior is combined with adverse childhood experiences. The literature also indicates that behavior is probably largely explained by additive genetic effects.
This might explain why the replication rate of studies investigating susceptibility genes continues to remain slow.

**Implications**

Behavioral genetic studies are under heavily debate in the scientific community. The ramifications of susceptibility-genes have even penetrated legal systems worldwide (BOX 3). Several criminal case studies, that involved a heritable tendency towards antisocial behavior, received worldwide media attention.

If behavioral genetic findings are ready to be taken into court, remains questionable. Moffitt, for instance, stated that the effects of the MAOA gene are known to vary between different ethnic groups. This also appears to be the case in other identified genetic polymorphisms (Moffitt et al., 2001). The genealogy of the criminal in question suddenly becomes relevant and the feasibility still needs to be addressed. Behavioral genetic studies also have only correlated genes indirectly to antisocial behavior. A direct effect can only be mediated through environmental experiences (BOX 4).

**BOX 4: James Fallon**- Neurobiologist with a genetic predisposition towards psychopathic antisocial behavior

Professor Fallon investigated the brain patterns of known serial killers and compared them to his own. He shockingly concluded that his limbic system, like the limbic systems of psychopathic killers, was not normally functioning and that displayed the exact same PET-scan patterns as these killers. He also appeared to have all known genetic variants that are risk factors for aggressive antisocial behavior. After self-observation, he came to realize and acknowledge that he had fundamental traits that are associated with psychopathy, however he never acted in a violent or criminal matter. His conclusion was that whether genes are triggered or not, all depends on what happens during childhood. Simply having the brain and genetics of a killer, does not necessarily makes one a killer. *(BBC’s Horizon documentary – “Are you good or evil?”* - Sept 7th 2011)

Individuals that experienced severe child abuse are also able to develop normal behavior, even if they have a genetic susceptibility towards antisocial behavior development. Where do we draw the line when it comes to adverse childhood experiences and can we prevent behavioral genetic implications from overindulgence in court?

The genes that have been implemented in court today, all cause non-additive genetic effects. Behavior however, is suspected to be largely determined by additive genetic effects and not by mere dominance deviance. Just because dominance deviance is easier to identify or label by no means implies that it poses as a higher risk factor for antisocial behavior. The legal system today, alters criminal convictions based on known genetic risk factors for antisocial behavior. Individuals with an identifiable genetic predisposition are therefore able to get a different sentence from individuals with a (as of yet) non-identifiable genetic predisposition. Lowering sentences due to genetic predispositions is not even necessarily logic, because those criminals might pose an even greater threat to society than criminals convicted of similar crimes that do not display natural tendencies towards antisocial behavior.

Whether people can or cannot help their natural tendencies and whether they are or are not capable of knowing the nature of their alleged criminal act, cannot be partially based on indecisive behavioral genetic studies.

Behavioral genetics remain bio-ethically difficult, because the the etiology of antisocial behavior has not been uncovered yet. It is therefore no wonder why findings in the area are subjected to much social debate. The most important dilemma in relation to legal proceedings today involves the amount of association with the development of antisocial behavior. But as long as the etiology of antisocial behavior has not been fully uncovered, the justification of taking genetic predispositions into consideration at legal proceedings is not entirely grounded nor fair. Genetic susceptibilities towards antisocial behavior, therefore need to be handled with much care and consideration in society today.

**References**


Blair RJR. The neurobiology of psychopathic traits in youths. Nature Reviews 2013;14:786-799


Lofrida C, Palumbo S, Pellegrini S. Molecular genetics and antisocial behavior: Where do we stand?. Experimental Biology and Medicine 2014;0:1-10


Pieri E and Levitt M. Risky individuals and the politics of genetic research into aggressiveness and violence. Bioethics 2008;22(9):509-518


Tuvblad C and Baker LA. Human Aggression Across the Lifespan: Genetic Propensities and Environmental Moderators. Advanced Genetics 2011;75:171-214

Yanowitch R and Coccaro EF. The Neurochemistry of Human Aggression. Advances in Genetics 2011;75:151-169