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Angelman Syndrome

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Abstract

Angelman Syndrome (AS) is a neurogenetic disorder that is classically characterized by excessive laughter and a happy demeanor. Aggression, sleep disorders and epilepsy are other phenotypes associated with this disorder as well. Both happy and aggressive demeanors have been expressed in five different consumers at The Kennedy Center, a site which offers programs and services to individuals with varying disabilities. Research proposes several different genetic mechanisms responsible for the development of AS, each of which impact the function of the UBE3A gene located in the 15q11-13 region on chromosome 15. Additionally, from an evolutionary perspective, Emotion Signaling Theory and Kinship Theory have been used to provide another explanation for the observed behaviors of those possessing Angelman Syndrome.

Physical and Behavioral Phenotypes

Angelman syndrome (AS) is a neurogenetic disorder which affects approximately 1 in 15,000 live births each year (Williams et al 2009). The disorder impacts brain development so profoundly, such that most individuals with AS fail to reach a developmental age of three years old (Gasca et al 2010). AS is sometimes referred to as the “Happy Puppet Syndrome,” because most individuals possessing AS tend to display a distinct set of physical and behavioral

phenotypes, including excessive laughter and a happy demeanor (Gasca et al 2010; Pelc et al 2008). These characteristics are manifested among five individuals with AS who participate in different programs and services offered at The Kennedy Center, a site where individuals with varying disabilities across all age groups can enroll in. While interning at the Kennedy Center, beginning in August 2014 through December 2014, I have observed five consumers, each possessing Angelman Syndrome. For privacy regulations, each consumer will be referred to as *consumer #1, #2, #3, #4, #5*.

The consumers at the Kennedy Center express other attributes in addition to the common physical and behavioral phenotypes generally associated with AS. Some physical characteristics I have noticed among each of the consumers are that some of the facial features are slightly malformed, including a protruding tongue and a wider spaced jaw frame (Gasca et al 2010).

Also, several behavioral characteristics that I have observed among the consumers with AS are that they are each non-verbal and have not developed a verbal vocabulary. Consumers #2 and #3 both display the typical qualities associated with AS, which is a constant happy demeanor, consisting of excessive smiling and laughing. On the other hand, consumers #4 and #5 express a very aggressive demeanor, which research has shown to be another common characteristic of AS (Strachan et al 2009). In particular, consumer #4 will grab anything he can reach with full force and strength. Even with his breaks locked on the wheelchair, he can use his bodily forces to relocate himself. Similarly, consumer #5 has displayed strong physical aggression and participates in many disruptive behaviors, such as bolting and running into other individuals and objects (The Kennedy Center 2014). He is very hyperactive and appears to smile when he receives something he wants. Furthermore, consumer #1 exhibits hypermotoric behavior as he has a tendency to flap his arms repeatedly, rarely smiles, and eats very quickly by

placing large amounts of food in his mouth at once. Although not observed at the Kennedy Center, epileptic seizures and sleep abnormalities are also qualities that are associated with AS (Van Buggenhout et al 2009).

Genetic mechanisms responsible for Angelman Syndrome

Significant research has been done on the genetic mechanisms that contribute to AS, and the UBE3A gene proves to have a strong correlation with the disorder. There are four different genetic mechanisms by which AS can develop, each contributing to different phenotypes and different levels of severity. They include large chromosome deletion, paternal uniparental disomy (UPD), imprinting defect (ID), or a mutation in the UBE3A gene itself (Williams et al 2009). Each of these mechanisms share a common feature, in that they each either disrupt, inactivate, or cause an absence of the UBE3A gene on the maternal chromosome 15 (Williams et al 2009).

The UBE3A gene encodes for the production of ubiquitin protein ligase, which is a critical enzyme that aids in protein degradation (Jana 2012). The enzymes attach a protein called ubiquitin to target damaged and unnecessary proteins for degradation by proteasomes, thereby helping to maintain normal cell function and development (Jana 2012). This gene also serves a critical function in regulating motor control, as the UBE3A gene influences axon guidance and neuronal connectivity via synapses (Oliver et al 2007). Development and brain function are further impacted by the UBE3A gene, because it also serves as a co-activator of steroid hormone receptors (Jana 2012).

Another significant feature of this particular gene is that it is located on both the maternally and paternally derived chromosome 15 (Williams et al 2009). However, this gene is

considered to be an “imprinted gene” because it experiences parent-specific activation in the brain neurons (Jana 2012). Despite the allele being present on both the maternal and paternal chromosomes, because it is imprinted, the paternal allele is silenced, thus neurons only utilize the active maternal UBE3A allele (Williams et al 2009). However, in non-neuronal tissues, the UBE3A allele is turned on in both the maternal and paternal chromosome 15, concluding that imprinting patterns of UBE3A are only expressed in neurons (Williams et al 2009).

Large chromosome deletion

Large chromosome deletion refers to the deletion of the 15q11-13 region on the maternally derived chromosome. More specifically, the 15q12 region is removed, which contains the active UBE3A gene, while the paternal allele is silenced due to genomic imprinting (Clayton-Smith and Laan 2003). The deletion of the active UBE3A gene inhibits the brain from undergoing necessary processes that aid in protein degradation. In effect, damaged cells fail to become degraded and synaptic regulation becomes disrupted, thus affecting the nervous system. Additionally, there are other genes located within the 15q12 region that are connected to speech development; hence the removal of such genes can provide an explanation for the lack of verbal speech observed in individuals with AS (Haig 2011).

Research suggests that those who acquire AS due to large chromosome deletion compared to another mechanism tend to display more severe seizures, ataxia and other motor difficulties, along with impaired language and cognitive development (Williams et al 2009). Each of these phenotypes can be impacted by the deletion of critical genes located in the 15q12 region on the maternal chromosome 15 which are necessary for proper speech and motor

development. Also, because neuronal pathways are disrupted due to the absence of the UBE3A gene, impaired motor control proves to be a likely result.

Paternal uniparental disomy

Paternal uniparental disomy results when a child inherits two paternal copies of chromosome 15 (Clayton-Smith and Laan 2003). Since the UBE3A gene is an imprinted gene, certain areas of the brain will have two inactive copies of the UBE3A gene, where it should normally be active on the maternal chromosome. As a result, certain brain regions do not have proper neuronal function because all pathways dependent upon the UBE3A gene now become disrupted and fail to proceed. Likewise, inheritance of two maternal copies of chromosome 15 results in a disorder called Prader-Willi syndrome (PWS), which is primarily characterized by obesity (Brown and Consedine 2004; Ubeda 2008). PWS is opposite to AS in that it is distinguished by a lack of expression of paternally inherited genes on chromosome 15, as opposed to a lack of maternally derived genes in AS (Brown and Consedine 2004).

Imprinting Defect

Imprinting defect results when both a maternal and paternal chromosome 15 is inherited, but the maternal copy functions as a paternally derived chromosome. In essence, the maternal chromosome contains an inactive copy of the UBE3A gene (Williams et al 2009).

Research proposes that ID results from DNA methylation at the AS imprinting center, which is a short DNA sequence located in the 15q12 region of the maternal chromosome 15 (Williams et al 2009). Normally, during embryo development, the UBE3A allele on the maternally inherited chromosome 15 is “imprinted,” or marked, to be turned on and active in the

brain neurons. Contrarily, the UBE3A allele on the paternally inherited chromosome 15 is imprinted to be turned off in the brain neurons, thus allowing for only maternal UBE3A expression in the brain (Williams et al 2009). Certain genes are directed to be marked as either active or inactive by the regulation of the imprinting center. However, in the case of imprinting defect, there appears to be heavy methylation at the imprinting center on the maternally derived chromosome 15, which prevents transcription and activation of the UBE3A gene. This results in two inactive copies of the UBE3A gene which disrupts neuronal processes dependent upon the gene, and hinders proper functioning of the nervous system (Williams et al 2009).

Research has shown that those who attain AS through UPD or ID tend to have less distinct facial malformations, less severe motor difficulties, and a lower frequency of seizures compared to those who attain AS through large chromosome deletion (Williams et al 2009). This could be due to the fact that genes located within the 15q11-13 region are not deleted in the occurrence of ID or UPD, whereas several genes in addition to the UBE3A gene are deleted in the incidence of large chromosome deletion. In effect, ID and UPD result in less severe phenotypes because genes responsible for motor control and neuronal signaling for example are still present and possibly functioning, whereas they are completely deleted in the case of large chromosome deletion.

UBE3A gene mutations

Finally, mutations on the UBE3A gene itself can cause AS. Research has shown that genetic defects with the UBE3A gene inherited from the father may not cause any problems in the child. However, a genetic defect inherited from the mother will result in AS in the child (Williams et al 2009). This phenomenon demonstrates imprinting effects, as the same gene has

different impacts depending on the parental origin. Because the maternal allele is active in brain neurons and silenced on the paternal chromosome, mutations on the maternal allele will carry out, while those on the paternal allele will remain silenced.

Also, research suggests that those who inherit a UBE3A mutation tend to express phenotypes of intermediate severity compared to the other proposed mechanisms. They can either express severe or less severe motor abnormalities, seizure occurrences, and either distinct or less distinct facial malformations (Williams et al 2009). This is likely due to the fact that the UBE3A gene is not completely inactive or deleted; rather it is only mutated, thus it is still functioning, but not optimally and accurately.

Animal and Insect models for AS

Although the current research does not provide enough information to explain exactly how each particular genetic mechanism contributes to a different phenotype, several mice and fly models have been developed in order to study AS in as much detail as possible. For instance, the most common mouse model studied is the UBE3A knockout mouse model (Jana 2012). Four groups were present within this particular model: wild type mice, a heterozygous maternal UBE3A deficient group, heterozygous paternal UBE3A deficient group, and homozygous mice (Jana 2012). The wild type mice possess both a maternal and paternal copy of the UBE3A gene. Both of the heterozygous groups contain both a maternal and paternal chromosome; however, the heterozygous maternal UBE3A deficient group lacks the UBE3A gene on the maternal chromosome, whereas the heterozygous paternal UBE3A deficient group lacks a UBE3A gene on the paternal chromosome. The homozygous group contains both a maternal and paternal chromosome; however, both chromosomes lack the UBE3A gene. Primarily, the researchers

observed that the maternal deficient mice expressed more ataxia and impaired motor control and memory, compared to the other groups (Jana 2012). Also, the maternal gene deficient mice showed an increased number of licks when eating, compared to the wild type mice (Jana 2012). In other words, the maternal gene deficient mice expressed rapid movement of the tongue, causing them to consume their food very quickly. This indicates that there is less synchrony between breathing and swallowing, which can explain the abnormal eating patterns of some AS individuals, such as consumer #1 (Jana 2012). This could be due to a lack of UBE3A gene activity in the cerebellum, a brain structure involved in motor control and synchronization (Jana 2012).

Additionally, the maternal gene deficient mice spent more time in the dark, which may be a sign of stress due to the absence of UBE3A, which acts as a co-activator of steroid hormones such as the glucocorticoid hormone receptor (Jana 2012). Glucocorticoid hormone regulates many genes that are responsible for development, metabolism and the immune response (Jana 2012). This hormone is also present in the mammalian stress response, and is associated with neurological disorders such as depression and anxiety (Jana 2012). Although researchers have not fully determined an exact mechanism by which the absence of UBE3A impacts the activation of glucocorticoid hormone receptor, based upon the current mouse models, it is proposed that the lack of UBE3A possibly fails to activate the hormone receptor, which may be responsible for the observed increases in stress and anxiety levels in the mice (Jana 2012). This particular mouse model further proves the importance of the UBE3A gene in proper neuronal activity, as synapses can become modified, altering several motor functions and generating neurological disorders. More research must be done to gain a clearer understanding of how exactly the absence of UBE3A regulates the glucocorticoid hormone receptor.

Second, another mouse model that has been studied used a gene knockout method, where the GABRB3 gene, GABA receptor B3 subunit, was deleted. The GABRB3 gene is located within the 15q11-13 region on chromosome 15, and is not considered to be an imprinted gene. In essence, it is not a direct cause of AS, but rather it serves as a contributing factor to the resulting phenotypes and their severity (Jana 2012). Researchers have linked the absence of this gene to more severe phenotypes, although the mechanisms by which it does so is unknown. The researchers observed very poor motor control, epilepsy, and learning difficulties in the experimental mice lacking the GABRB3 gene, compared to the control mice containing the gene (Jana 2012). This gene acts as a receptor for many different neurotransmitters, so the deletion of the 15q11-13 region, which thereby deletes the GABRB3 gene, strongly influences the nervous system because certain neurotransmitters are not recognized by the GABRB3 gene and fail to produce an action potential (Jana 2012).

Alternatively, a fly model using *Drosophila* flies was developed to study the dUBE3A gene, which is homologous to the human UBE3A gene. Although the flies did not show any morphological phenotypes, they did express many abnormal motor functions (Jana 2012). They also observed that both over expression and under expression of the dUBE3A gene results in reduced formations of terminal dendrite branching (Jana 2012). Therefore, this fly model can serve as a beneficial model for studying the role of UBE3A in dendrite formation and how it impacts motor control.

Emotion Signaling Theory

The Emotion Signaling Theory along with the Kinship Theory have also been used to provide explanations for the observed behaviors and phenotypes in individuals with AS.

Excessive laughter along with a happy demeanor appears to be the primary phenotype for depicting AS. Due to being such a complex neurodevelopmental disorder, it becomes difficult to directly explain the cause of behaviors such as excessive laughter and a happy demeanor from a genetic standpoint. As a result, both the Emotion Signaling Theory along with Kinship Theory has been developed in attempt to provide an explanation for the observed behaviors. Emotion Signaling Theory explains communication between individuals through different emotional signals (Oliver et al 2007). For example, in regards to AS, high levels of social contact can be responsible for the observed happy demeanor and excessive smiling (Oliver et al 2007). In one particular study, researchers studied the effect of ongoing social contact in eliciting smiling in subjects with AS. The experimental group experienced constant social interaction, whereas the control group was placed in a non-social environment. The results indicated that the AS individuals in the experimental group laughed and smiled more when there was ongoing social interaction, as opposed to the subjects in the control group with no social interaction (Oliver et al 2007). In this particular study, the smile served as a signal to the receiver, represented by the adult. In response to the smile, the adults smiled back, thus allowing for the social contact to be maintained (Oliver et al 2007). The emotion of "happiness" serves as the signal to initiate a response from the receiver, and in this case the response is a smile in return, along with social interaction. Therefore, researchers concluded that individuals with AS may smile excessively to not only attract attention, but also to maintain it, as it may provide a sense of reward to the individual (Oliver et al 2007).

Researchers have linked the Emotion Signaling Theory to aggressive behavior as a way to attract attention as well (Strachan et al 2009). Aggression may be positively reinforced if more attention is given to the consumer and maintained as a result of such behavior (Strachan et al

2009). This could explain the aggressive demeanor observed in consumers #4 and #5, in that they may seek attention through destructive actions which would require close attention from the staff.

Another possible solution for the aggressive behaviors seen in consumers #4 and #5 could be a result of possible anxiety. Through the study of mice models deficient in the UBE3A gene on the maternal chromosome, some mice experienced high levels of stress and anxiety due to the absence of the UBE3A gene, which is a co-activator of the glucocorticoid hormone receptor (Jana 2012). Experimental results indicate that mice possessing a deletion of the maternal UBE3A gene spent more time in the dark and had impaired contextual fear, compared to the mice without a maternal UBE3A knockout (Jana 2012). For example, hyperactivity, aggression, and abnormal sleep patterns tend to be behaviors generally associated with anxiety. Thus, individuals with AS may have anxiety, and in response, may seek attention levels or act aggressively.

Kinship Theory

Kinship Theory, which is also referred to as the Maternal Investment Theory, provides further explanation for the observed behaviors in those with AS (Strachan et al 2009). Kinship Theory is used in conjunction with genomic imprinting, which correlates a particular phenotype as being dependent upon maternal or paternal inheritance (Pelc et al 2008). The same gene, which is referred to as an imprinted gene, is present on both the maternal and paternal chromosome; however, its expression is dependent upon which parental chromosome the gene is located on (Haig 2011; Strachan et al 2009).

The Kinship Theory argues that genes inherited both paternally and maternally are expressed differently in order to favor the continuation of the maternal or paternal chromosomes (Strachan et al 2009). For instance, the paternally inherited gene seeks to demand the allocation of maternal resources for offspring, because that will in turn increase the probability of survival, hence passing on paternal genes to future generations (Strachan et al 2009; Ubeda 2008). Conversely, the maternal allele seeks a lower amount of maternal investment, because less energy expended by the mother maintains enough energy to support future births and pass on the maternal genes to future generations (Strachan et al 2009; Ubeda 2008). The allocation of maternal resources presents fitness costs to the mother, and fitness advantages to the signaler (Brown and Consedine 2004).

Kinship Theory is based largely upon Emotion Signaling Theory because social contact indicates parental investment (Strachan et al 2009). Therefore, because individuals with AS possess two paternal chromosome15, or have a mutated maternal chromosome 15, the paternal genes will favor more maternal investment. In turn, there are more maternal costs, which will provide an advantage to the paternal genes to survive and pass on to future generations (Strachan et al 2009; Ubeda 2008). From an evolutionary perspective, social interaction indicates a greater level of maternal investment, as the mother nurtures the offspring before birth, and can provide the essential nutrients after birth through breast feeding and other methods (Strachan et al 2009; Ubeda 2008). Those with AS seek more attention from adults through the behaviors of smiling, laughing, and aggression, because the paternal genes favor maternal investment, of which social interaction is categorized under according to evolutionary theory. Likewise, Kinship Theory may propose that those possessing PWS excessively eat because they feel obligated to obtain

nutritional resources that the mother failed to provide for them, which may in turn generate a feeling of neglect that can be overcome by the satisfaction of eating.

Conclusion

In all, both genetic disruptions of the UBE3A gene on the maternal chromosome 15 along with Emotion Signaling Theory and Kinship Theory provide explanations for the observed phenotypes expressed in those with AS. Although the Emotion Signaling Theory and Kinship Theory both provide legitimate arguments, they do not serve as effective theories to apply to all cases. Each individual expresses AS differently, some more severe than others. Research has suggested that some individuals with AS have an affinity towards water, which I have also observed in consumer #5 (Brown and Consedine 2004). Taking a liking towards water does not appear to be a maternal resource, therefore weakening this theory.

Also, the Emotion Signaling Theory and the Kinship Theory are both very complex and based heavily on evolutionary theory, which makes it difficult to discretely prove several claims. Although it is plausible to conclude that smiling is used as a way to attract social attention, there are many AS consumers who rarely smile, such as consumers #1, #4, and #5, each of which are males. Contrarily, the females, consumers #2 and #3 constantly smile and express a happy demeanor. More research needs to be done in regards to gender and AS because there may be certain genes present in each gender which can impact emotions and phenotypes.

Additionally, the frequency of smiling can also be affected by the environment in which the individuals live in. Levels of frustration, poor versus a healthy home life, and overall genetics can each influence one's emotions and affect the frequency of smiling. Since several neurological pathways are interrupted due to mutations or alterations of the UBE3A gene, there

may be a particular pathway that stimulates certain nerves to constantly produce a smiling phenotype. The UBE3A gene plays a critical role in axon firing; therefore it can be possible that alterations in this gene can impact the nerve signaling which stimulates a smile.

Finally, consumer #1 is a male who rarely smiles. He flaps his arms constantly, eats very quickly, but does not seem to demand much attention from others. Consumer #1 entered the Kennedy Center at 18 years old, and is now 23 years old. When he first entered the program at the Kennedy Center, he smiled and laughed very frequently and displayed a different demeanor. Research suggests that age may also play a role in the happy demeanor expressed and not expressed in many individuals possessing AS (Strachan et al 2009). As consumer #1 aged, his behavior seemed to mellow out. While at the Kennedy Center, consumer #1 is placed on behavior plan, which requires a great deal of staff intervention to redirect any disruptive behaviors (The Kennedy Center 2013). Such attention may have conditioned him to act differently, and resulted in a more reserved personality. It is currently unknown if a particular biological pathway impacted the change in behavior, or if it was simply due to the behavior plan used at the Kennedy Center. Similarly, one particular research study also observed that younger individuals with AS between the ages of two years old and sixteen years old expressed a pronounced happy demeanor, while those who were older, smiled less frequently (Strachan et al 2009). It is unknown however, if this was a result of a particular biological mechanism, or a gradual change in emotional state as they age.

Based upon all of the research, including UBE3A mutations, Emotion Signaling Theory, and Kinship Theory, I propose that the observed phenotypes associated with AS are due to mutations in the UBE3A gene, which disrupts several different pathways that regulate emotions, motor control, and other behaviors. Kinship and Emotional Signaling theories seem plausible,

but they lack discrete proof. Since the alterations of the UBE3A gene impact several different neurological processes, smiling may either increase or decrease, depending on which pathways are disrupted and which hormone receptors prove to be lacking. Therefore, by focusing more intently on the genetic pathways impacted by the UBE3A gene and how its absence affects other genes, researchers can gain more insight into the causes of the varying degrees of severity and phenotypes seen in individuals with AS.

Undoubtedly much more research needs to be generated in order to understand AS and the processes that lead to the observed phenotypes. Several factors can impact an aggressive or happy demeanor, such as home life, genetics, gender, and age. It is likely that each of these factors work together to produce a phenotype, therefore no single reason can be generated to explain the observed behaviors. Likewise, because each individual expresses the phenotypes of AS at different degrees of severity, one theory cannot be applied to every individual, because each individual experiences different environmental influences and different genetic backgrounds.

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