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Review Article

Angelman Syndrome: An Autism Spectrum Disorder

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Neurodevelopmental disorders limit the mental, physical, and social lives of affected individuals and their families. These disorders are often related to genetic abnormalities having a distinct chromosomal location. The abnormalities can cause incorrect proteins to be formed or biochemical pathways to be blocked, predominately affecting brain development, but also having pleiotropic effects. Research into defining and correcting these genetic abnormalities is important to help distinguish between unique neurodevelopmental disorders so that proper clinical interventions are available for affected individuals. In the following review, Angelman syndrome, which results from *UBE3A* gene function being lost at maternal chromosome 15q11.2-q13, will be discussed. Angelman patients suffer from the defining characteristics of speech impairment, uncontrolled laughing and smiling, motor development issues, muscle tension, and possible ataxia. The genetic mechanisms of the disorder as well as possible therapies will be discussed, with future areas of research into genetic therapies to treat Angelman syndrome also put forth. Research into Angelman syndrome can provide an avenue for a clearer understanding of other neurodevelopmental disorders.

Keywords: Angelman syndrome, autism spectrum, *UBE3A*, maternal chromosome 15, neurodevelopmental disorder

Introduction

Angelman syndrome (AS) is a neuro-genetic disorder that is often mischaracterized as either profound autism or cerebral palsy. AS was first described in 1965 by Dr. Harry Angelman (reviewed by Martins-Tyler *et al.*, 2014) based on his observations of three young patients affected by severe intellectual disability, microcephaly, developmental delay, speech impairment, lower motor skills, inappropriate laughter, and ataxia (loss of full control of body movements) (reviewed by Williams *et al.*, 2010). Later studies determined the phenotypic characteristics of AS are caused by loss-of-function of the *ubiquitin ligase E3A* (*UBE3A*) gene on maternal chromosome 15q11.2-q13 (Bailus and Segal, 2014). As a result of *UBE3A* being suppressed, or mutated, the ubiquitin-proteasome pathway is disrupted leading to loss of proper functioning of many organ systems, specifically brain neurons (Peters *et al.*, 2009).

Smith and coworkers (2003) reported an incidence rate for AS at ~ 1 in 10,000 newborns. The incidence rate has changed drastically since the time of Harry Angelman as it occurred in 1 in 40,000 live births before better diagnostics, clinical phenotyping, and molecular genotyping increased accuracy. Genotypic testing is necessary to distinguish AS from phenocopies such as individuals affected by Mowat-Wilson syndrome, caused by loss-of-heterozygosity at the *ZEB2* locus, and Christianson syndrome, an X-linked disorder with mutations in the *SLC9A6I* locus (Williams *et al.*, 2010). However, in 10% of patients with phenotypic AS, there is no known genetic mechanism. Because AS and its sister disorder Prader-Willi syndrome (PWS) result from abnormal imprinting regulation, approximately 78% of genotypic testing conducted analyzes DNA methylation patterns at the 15q11.2-q13 chromosomal region (Smith and Laan, 2003; Strachan *et al.*, 2015). These tests have a high success rate of determining if a patient has AS instead of a phenocopy or related neuro-disorder.

AS is much like other neuro-degenerative disorders in that there is a delay in brain development affecting mental, emotional, and social aspects of affected individuals. AS differs in that it is common for ataxia to occur and/or motor skills to be suppressed (Smith and Laan, 2003). PWS affects the same region of chromosome 15 as AS but requires lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. PWS clinically manifests as mild intellectual disability and hyperphagia. However, because clinical manifestations are age dependent, the primary methodology to distinguish the two syndromes apart is by DNA methylation analysis (Angulo *et al*., 2015). Other autism spectrum disorders, including "pseudo-AS", depend on deletions mapped to other chromosomes, including 2q23.1. Pseudo-AS behaves similarly to AS; deletions knock out genes regulating pathways important in normal brain and muscle development and function (Mullegama *et al*., 2014).

Molecular Genetics of AS

The primary cause of AS, ~75% of cases, is a *de novo* 3.08 Mb interstitial deletion encompassing the *UBE3A* gene at maternal 15q13.1-13.3 and affecting 15 other flanking genes regulating language development (Pettigrew *et al*., 2015; Ranasinghe *et al*., 2015). Once a couple has a child with this *de novo* deletion causing AS, the chances of having another child with this deletion falls dramatically to ≤ 1%; each birth is an independent event. However, the high probability (1%) of the same mutation occurring in a sib encompasses the possibilities of either germ line mosaicism for the deletion or a balanced translocation in the mother (Williams *et al*., 2010). Microdeletions and other genetic abnormalities can be tested prenatally in the fetus and can lead to a genotypic diagnosis for AS; as with all genetic testing technologies, these data allow the parents to either terminate the pregnancy or prepare mentally and/or financially to care for a child having a genetic disorder (Wapner *et al*., 2015). The deletion or point mutation, usually leading to protein truncation, of *UBE3A* is the main cause of AS; therefore, detecting these genetic abnormalities is the main focus of research into prenatal testing for this disorder. These genetic testing technologies are also beneficial as an independent methodology for estimating incidence rates. However, ~10% of patients clinically categorized with AS have no genetic inconsistencies in maternal chromosome 15;

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as a result, an incorrect diagnosis for another autism spectrum disorder or similar brain development disorder, as mentioned above, can occur, leading to incorrect treatment modalities (Smith and Laan, 2003).

Deletion or inactivation of *UBE3A*, encoding E6-associated protein (UBE3A/E6AP), defines AS from other similar syndromes (Li and Qui, 2014; Mandel-Brehm *et al*., 2015). UBE3A/E6AP is an E3 ubiquitin ligase that conjugates ubiquitin groups to specific proteins targeting them to the proteasome for degradation (Sell and Margolis, 2015). The S5a subunit of the proteasome tethers ubiquinated protein to the proteasome in preparation for proteolysis. S5a is mono-ubiquinated by UBE3A/E6AP decreasing the enzymatic activity of the proteasome. In UBE3A/E6AP deficient cells, not only are substrates of UBE3A/E6AP not ubiquinated, but the activity of the proteasome is perturbed (Tomaic and Banks, 2015).

Molecular genetic analysis reveals that in mammals, the paternal allele of *UBE3A* is silenced by genomic imprinting in neurons. Imprinting is the phenomenon by which specific genes are expressed based on the parental chromosome inherited. In the case of *UBE3A*, the paternal copy is silenced in the brain by an antisense RNA, *UBE3A-ATS*, expressed from the paternally inherited chromosome (Meng *et al.*, 2013; Strachan *et al*., 2015). Because the imprinting of *UBE3A* is evolutionarily conserved, the mouse ortholog, *Ube3a*, can be genetically manipulated to recapitulate AS in mice. To this end, transgenic maternally deficient *Ube3a* mice (*Ube3a*$^{m-/p+}$) were created to test the hypothesis that lack of maternal expression of the *Ube3a* allele is necessary and sufficient to cause AS. These mice exhibit AS pathogenesis confirming the hypothesis that maternal *Ube3A* deficiency is the cause of AS in mice and by extension, humans (Li and Qui, 2014). The converse experiment was carried out in another AS mouse model (*Ube3a*^{KO}), where activating the paternal allele in neurons via the depletion of *UBE3A-ATS* antisense RNA reversed many disorder-related symptoms of AS including motor coordination defects, cognitive deficit, and impaired long-term neuronal potentiation (Meng *et al*., 2013).

A confounding factor in understanding the molecular genetics of AS and developing molecular therapeutics is the heterogeneity of paternal *Ube3a* expression in the mouse nervous system. In contrast to other neurodevelopmental disorders, AS symptoms do not manifest in humans until 6 to 12 months of age. This clinical phenotype could be partially explained by the observation that in the *Ube3a*$^{m-/p+}$ AS mouse model, incomplete imprinting (i.e. some biallelic expression) of *Ube3a* was observed in the postnatal developing cortex, but not in subcortical and cerebellar regions where neurogenesis and migration is mostly complete. For example, there is biallelic expression of *Ube3a* in the early postnatal cortex of the brain and in glial cells, such as astrocytes and oligodendrocytes (Grier *et al*., 2015; Martins-Tyler *et al*., 2014). The precise mechanism by which loss of maternally expressed *UBE3A* in neurons causes AS is still unclear. However, the expression of many cell membrane associated proteins and kinases, including activity-regulated cytoskeleton-associated protein (ARC), ANKYRIN-G, NAV1.6, and CAMKII are up-regulated in AS mice; whether they are direct targets of UBE3A/E6AP, or affected indirectly, is not known. Interestingly, abnormal brain activity, but not motor behaviors or communication, in AS mice is rescued by decreasing expression of the synaptic protein ARC. These data demonstrate the complexity of the neural circuits defective in AS and the multipronged approach needed to develop clinical therapies to treat this disorder (Mandel-Brehm *et al*., 2015).

Uniparental disomy (UPD) causes ~ 5-10% of AS cases. UPD arises when a zygote develops in which both copies of one particular chromosome are inherited from one parent. UPD most often occurs from a trisomic conceptus, a zygote that has received two homologous chromosomes from one parent and a single chromosome from the other parent. Loss of the single chromosome copy soon after first cleavage results in heterodisomy. Alternatively, a monosomic zygote is rescued by duplication of the single chromosome, resulting in isodisomy (two identical copies of a chromosome; Strachan *et al.*, 2015). Paternal UPD 15 results in a lack of expression of *UBE3A* in neurons. The majority of UPD AS cases are caused by paternal isodisomy 15 (Smith and Laan, 2003). UPD induced AS symptoms are not as severe as those cases resulting from deletions or point mutations; thus, a lower percentage of patients experience seizures and seizures that do occur are milder (Angulo *et al*., 2015; Williams *et al*., 2010).

Detection

Detection of Angelman has changed dramatically over the years ranging from genetic, anatomical, and physiological tests to determine if a patient suffers from *UBE3A* suppression. Electroencephalography (EEG) is commonly used to detect seizures in AS patients with 85% of affected children developing seizures by age three (Ranasinghe *et al*., 2015). Seizures persist into adulthood usually showing a decrease in frequency and intensity. Slow waves of high voltage are reported in patients with AS corresponding to abnormalities in the brain. An interesting observation demonstrated that even after seizures were controlled, the EEG patterns stayed the same, indicating an organic brain defect (Park *et al*., 2012). EEG patterns as well as other non-invasive tests such as MRI and CT scans help to determine abnormal brain patterns in patients (Gilboa and Tsar, 2013).

Detecting micro-deletions by standard karyotyping is technologically challenging due to the miniscule differences that are made in the genetic code. Geneticists are able to diagnose micro-deletions at 15q11.2-q13 in AS patients by fluorescence *in situ* hybridization (FISH) using probes such as D15S10 and *SNRPN* that are adjacent to the *UBE3A* locus. Being able to understand the microdeletions that have taken place leads to a better understanding of which genes are involved in AS. However, clinical genetic testing is often done before testing patients using the FISH method due to cost and ease. (Bailus and Segal, 2014; Halder *et al.*,2015; Yokoyama *et al*., 2015).

Genetic testing is often able to correctly identify AS but physical traits allow clinicians to presumptively identify the syndrome. Throughout the world there have been specific tests and studies performed on the effects of AS in the lives of patients (Khouzani *et al*., 2014; Park *et al*., 2012). A study of Iranian AS patients revealed severe intellectual disabilities, a clear aberration from the average Iranian citizen, generating negative effects on patients in their social and emotional lives (Khouzani *et al*., 2014). In a South Korean study, seizures were detected in patients at about age 2. These debilitating seizures damage a patient's brain, causing memory loss

and/or paralysis in addition to congenital AS symptoms (Park *et al*., 2012).

Patients with AS also suffer from physical disabilities such as obesity, muscle tension, and growth retardation. The obesity phenotype was studied in the *patDp/+* transgenic mouse autism model; modified with a 6.3 Mb paternally inherited interstitial duplication orthologous to the human 15q11–q13 region (mouse chromosome 7). Paternal duplication of this chromosomal region recapitulates the only known recurrent cytogenetic abnormality in humans affected with autism spectrum disorder (~5% of cases). Why the interstitial paternally derived duplication causes stereotypical autistic behaviors in mice is unknown; regardless, microarray gene expression profiling determined that obesity in these mice correlated with regulatory gene networks involved in lipid metabolism being created as a result of *Ube3a* suppression (Liu *et al*., 2015). In social situations, obesity combined with motor suppression and possible ataxia are ways non-affected individuals can see abnormalities by simply looking at an affected individual (Williams *et al*., 2010).

Cognition in AS patients is negatively affected by lack of synaptic pathways key to normal mental functioning. The small-conductance potassium channel (SK2), which has a key role in synaptic plasticity and memory, is directly ubiquitinated by UBE3A/E6AP, initiating endocytosis and degradation by the proteasome. Therefore, when *UBE3A* activity is lost, brain function is severely compromised. Loss of *UBE3A* also leads to a large amount of SK2 in the hippocampus of the brain; when neuronal pathways in the hippocampus are interrupted, memory is inhibited and the absence of the orchestration of memory playback and normal functioning leads to social, mental, and intellectual disability as seen in AS individuals. (Sun *et al.,* 2015; Lizarraga and Morrow, 2015).

Therapy

Researchers are investigating therapies and possible cures for AS which are minimally invasive, patient specific, and have low toxicity. An example is gene expression therapy, which is ideal since AS is a monogenic disorder. One way that researchers are approaching this is through DNA-binding protein engineering; these proteins can act either as activators or repressors by fusing them to transcriptional or epigenetic effector domains creating an artificial transcription factor (ATF). For *UBE3A*, an ATF could be used to either reactivate the silenced paternal *UBE3A* or inhibit expression of *UBE3A-ATS* antisense transcript in neuronal cells. Any genetic therapy specifically targeted to the brain has to bypass the blood brain barrier. Current approaches, tested in AS mouse models, include direct intracranial injection and delivery using retroviral vectors (Bailus and Segal, 2014). Currently, AS symptoms are managed by drug therapy to treat gastrointestinal disorders, seizures, and hyperactivity; concomitantly, the patient undergoes occupational, physical, and speech therapy for developmental delay, ataxia, and improving nonverbal communication modalities (Williams *et al*., 2010). The reasoning behind nonverbal communication is that most patients have a minimal number of words they are able to use to communicate (Yokoyama *et al*., 2015). Furthermore, some researchers have primarily characterized AS by the characteristic lack of speech seen in patients (Germain, 2014).

Neurodevelopmental Disorders and Autism Spectrum

Neurological disorders that lie on the autism spectrum range greatly in severity, causing controversy in both defining autism as well as how one talks about autism. The term "autism", coined by the Swiss psychiatrist Eugene Bleuler in 1910, is derived from the Greek word for self, "autos", and describes a condition in which individuals remove themselves from social interaction, becoming, literally, an "isolated self". Dr. Bleuler used the term to refer to a group of symptoms in his patients diagnosed with schizophrenia (Kuhn, 2004). Dr. Leo Kanner, in a landmark paper, adopted the term "autism" to explain the behavior of several children he treated who acted withdrawn (Kanner, 1943). His definition was based off of the patients he saw in his clinic, leading to great debate on how he defined autism, as it became clear over time that his definition was too narrow. His work also led, circuitously, to the overarching debate on social disabilities. The current understanding of autism spectrum allows for two broad categories: functional and disabling. Typically, Asperger syndrome and classical autism fall in the functional category as there is not significant disability in speech or mental changes. On the other end of the spectrum, AS, PWS, and Rett syndrome (chromosome remodeling mutation on X chromosome) fall into the disabling category of autism. Furthermore, these syndromes often require a full diagnosis beyond clinical manifestations as they are the result of known genetic abnormalities in the patient (Strachan *et al.*, 2015; Rangasamy *et al*., 2013). The continuum of diagnosis covers varying levels of disability ranging from normal functioning to completely debilitating, allowing for unique treatments based on criteria used to place the patient on the autism spectrum.

Defining the discrepancy between disorders on the autism spectrum with unrelated neurodevelopmental disorders is not necessarily clear. Each disorder comes with exclusive characteristics which in turn impact the lives of affected patients. Neurodevelopmental disorders go beyond the autism spectrum and include Down syndrome (trisomy 21), Kabuki syndrome (dominant mutation in the *KMT2D* gene on X chromosome affecting global gene expression) and fragile X mental retardation syndrome (CGG trinucleotide repeats at Xq27.3 disrupting expression of at least three genes) among others (Strachan *et al.*, 2015; Rangasamy *et al*., 2013). These disorders are often more severe than autism as they can include a full chromosome being added as with Down syndrome. However, the characteristic that allows for AS to be classified as an autism spectrum disorder, is that it not only affects neurodevelopment, but also speech and communication with others (Veltman *et al*., 2005). The communication aspect of AS has classically allowed for its definition on the autism spectrum, although many other individuals with a non-autism disorder also have significant issues with communication.

Prospectus

Research still remains the most important step in the future of treating Angelman syndrome as there is currently no cure. With many biochemical and genetic research tools being created, it is not radical to predict that the burdens of AS can be alleviated. One such genetic tool, that is currently at the

forefront of biotechnological innovation, is CRISPR-Cas9, a gene editing system in which the genetic code is essentially cut open and rewritten to either wildtype or to create a favorable edit. AS, often being a result of a *de novo* deletion, can serve as a prime example of a disorder which CRISPR-Cas9 has been engineered by biotechnologists to repair. Researchers can hopefully fix the genetic code in which the deletion is corrected and the wildtype sequence added back. This will likely cause the UBE3A/E6AP protein to be expressed at wildtype levels. Thus, symptoms are likely to be lessened or even abrogated. With the correction of *UBE3A*, it is not out of the question whether AS can become a disorder that is eradicated in the near future. However, research is still taking place and testing on humans having genetic disorders is still in its infancy. CRISPR-Cas9 has the potential to alleviate AS but this still lies as potential and not reality at this time.

However, the CRISPR-Cas9 technology has many questions surrounding both its delivery and efficacy. Since CRISPR-Cas9 edits the genetic code, it is essential that each cell contains the edit. Over time, this can naturally occur as cells divide and the edits spread to other cells. However, with AS primarily affecting the neurons in the hippocampus, the edits would primarily need to exist in the neuronal pathways of the brain (see Therapy). We hypothesize that intracranial injection of a neuronal specific viral vector (e.g. herpes simplex virus type-1) could deliver the CRISPR-Cas9 cassette to the hippocampus, thus overcoming the blood brain barrier. CRISPR-CAS9 would then edit the genetic code of the infected neuronal cells. We do not currently know if this procedure is to be performed prenatally or post birth and still lies as an important question to answer. However, using CRISPR-Cas9 to edit the germ line of prospective parents would not be helpful as > 99% of mutations which cause AS are *de novo* (Williams *et al*., 2010). Another major question to address is that of efficacy. Genetic mosaicism remains a major problem within CRISPR-Cas9 edited cells (Reyes *et al.,* 2017). Prenatally, if the edits are not finished before the cells divide, the tissue would only be partially edited. Therefore, all, some, or none of the symptoms would be alleviated. Until this problem is fixed, implementing CRISPR-Cas9 remains a challenge not only in AS patients but all individuals suffering a debilitating genetic disorder. CRISPR-Cas9 has the potential to be the most important breakthrough for AS patients. The possibilities of editing the deletions which cause AS are in many ways, never before seen. CRISPR-Cas9 can be the primary treatment in the future but until the questions surrounding delivery and efficacy are answered, the cure is still far away.

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