Global Journal of Clinical Medicine and Medical Research [GJCMMR]
ISSN: 2583-987X (Online)
Abbreviated key title: Glob.J.Clinic.Medici.Medica.Res.
Frequency: Monthly
Published By GSAR Publishers
Journal Homepage Link- https://gsarpublishers.com/journal-gjcmmr-home/

The direction of treatment for imprinting disorders: A focus on Prader-Willi and Angelman Syndrome

BY

Noelle Dayal[1,2], Rebecca Freed[2,3], Marc Jackson[2,4], Daryoush Nejad[2,3], & Zachary I. Merhavy[1]*

[1]Ross University School of Medicine, Bridgetown, Barbados BB11093
[2]Georgetown University, Biomedical Graduate Education, Washington D.C., USA 20057
[3]Georgetown University School of Medicine, Washington D.C., USA 20007
[4]Medical University of South Carolina, Charleston, SC, USA 29425

Article History

Received: 14/02/2024
Accepted: 19/02/2024
Published: 20/02/2024

Vol – 2 Issue – 2

PP: -09-15

Abstract

Imprinting Disorders are a group of congenital pathologies that arise from defects in epigenetic programming or genomic imprinting. Treatments of these disorders today are based primarily on symptomatic management indicating a need for further research into potential epigenetic therapies. There is a lack of focus into worthwhile permanent solutions for these disorders. In this review, we discuss the role of imprinting in congenital defects and use Prader-Willi and Angelman syndrome as examples of imprinting disorders to show the imprinting mechanisms that lead to their phenotypic expression, their clinical manifestations, the importance and impact that early identification has, and the current standard of care. Recent research exploring epigenetic and gene-targeted therapies for imprinting disorders have shown promise as future routes to chromosomally targeted therapies for patients impacted by imprinting disorders. Topoisomerase inhibitors are an area of interest and were found to induce expression in a clinically silent gene in Angelman syndrome. Histone methyltransferase (G9a) inhibitors are another potential epigenetic therapy for Prader-Willi Syndrome as a way to induce expression of silenced genes on the maternal allele. Additionally, the use of an adeno-associated virus as a vector for delivery of DNA sequences has shown promise in patients with spinal muscular atrophy and could prove to be effective in the treatment of imprinting disorders. These new avenues of potential care are promising targets for future research that have the potential to lay the foundation for novel gene-targeted therapies.

Keywords: *#Angelman; #Genetics; #Imprinting; #MedicalGenetics; #MedicalTreatment; #Prader-Willi*

INTRODUCTION

Prader-Willi and Angelman syndrome are two diseases subcategorized within a group of disorders called imprinting disorders. Imprinting disorders are a family of congenital diseases characterized by overlapping clinical features affecting growth, development, and metabolism, which arise from molecular changes affecting imprinted chromosomal regions and genes. Genomic imprinting is the term used to describe the epigenetic reprogramming wherein one allele is expressed while the other allele is silenced in a parent-of-origin manner to ensure specific gene expression (Eggermann et al. 2015). In Prader-Willi and Angelman syndrome there is an abnormality in a specific segment of chromosome 15, the q11-q13 region, in either the paternally or maternally inherited copy, leading to a loss of function of several genes which likely explain the distinctive features of these conditions. These changes occur randomly during spermatogenesis and oogenesis or in early embryonic development, they are rarely inherited and do not tend to run in families (National Institutes of Health, 2022). DNA methylation, post-translational histone modification, chromatin structure, and non-coding RNAs describe the common epigenetic control of imprinted loci. DNA methylation serves to silence allele expression, through the reversible addition of a methyl group on cytosine bases at 5'-cytosine-guanine-3' regions, known collectively as CpG islands. Once either parent's allele has been methylated, the gene is considered imprinted. As the embryo goes through development, these epigenetic changes are maintained

*Corresponding Author: **Zachary I. Merhavy**

through the cell line (Pianka et al. 2018). DNA methylation is the mechanism that most commonly underlies Prader-Willi and Angelman syndrome, though in two distinct patterns, a maternally silenced allele or a paternally silenced allele in the 15q11-q13, respectively. Abnormalities in these imprinting processes are the root cause of imprinting disorders. Because of the complex genetic and epigenetic basis underlying these conditions, the current treatment for imprinting disorders, including Prader-Willi and Angelman syndrome, is focused almost entirely on symptomatic management.

Commonly characterized by hypotonia, hypogonadism, and growth hormone insufficiency (National Institutes of Health, 2022), the standard treatment for Prader-Willi syndrome includes growth hormone and oxytocin replacement therapy, which have shown promise in the symptomatic management of the disease (Pianka et al. 2018). Similar symptomatic management has been achieved for Angelman syndrome with behavioral, communicative, and physical therapy, which address the notable and significant symptoms of developmental disabilities, speech impairments, and balance disorders (National Institutes of Health, 2022). However, despite the success these therapies have had in managing the symptoms of these conditions, their efficacy cannot be generalized to the entire patient population given the various genetic and associated phenotypic variations of these conditions, including those which have not yet been characterized (Pianka et al. 2018).

Given the underlying causes of imprinting disorders, further understanding of epigenetic processes and the loci involved in these disorders are important topics of future research and will be fundamental in the development of curative treatments that target defective imprinting mechanisms. Significant progress has been made in recent years addressing these complexities. Here, we present a summary of the current experiments and topics being explored in the treatment of Prader-Willi and Angelman syndrome. Our discussion will describe the imprinting mechanisms underlying Prader-Willi and Angelman syndrome, discuss the current standard of care for these pathologies, summarize the recently published experiments and associated literature, as well as propose what appear to be promising future targets for research that could lead to therapies that not only improve the symptomatic management of these diseases but also provide the framework for novel gene-targeted therapies. Most notably, we will consider and explore the capability of topoisomerase inhibitors, Histone methyltransferase (G9a) inhibitors, and an adeno-associated viral vector as potential future targets for imprinting disorder therapies, specifically considering Prader-Willi and Angelman syndrome.

Imprinting Disorders

Prader-Willi

Prader-Willi Syndrome (PWS) is an imprinting disorder with many neurological, behavioral, and physical complications. People who have PWS might have hypothalamic dysfunction, aggression, hypogonadism, short stature, hypotonia during infancy, and hyperphagia, which can lead to obesity (Festen et al. 2008), as well as autism and psychosis characterized by hallucinations and paranoia (Crespi et al. 2018). Its estimated prevalence ranges from 1:15,000 to 1:30,000, and every person who is affected by Prader-Willi Syndrome has a unique set of symptoms and pathologies (Pianka et al. 2018).

Prader-Willi Syndrome results from a lack of a functional paternal copy of the 15q11-q13 region of chromosome 15. The 15q11-q13 region (as shown in Figure 1) contains many paternally expressed genes (PEGs) such as *MAGEL2*, *NDN*, *SNURF-SNRPN*, and a cluster of genes involving the expression of snoRNAs called the *SNORD116* cluster (Salminen et al. 2020). The exact function of these genes is still unclear, however, low *MAGEL2* and *NDN* expression has been associated with psychosis traits such as paranoia and hallucinations (Crespi et al. 2018). The *SNORD116* cluster has been found to express snoRNAs, which are small RNA segments that modulate genetic expression, particularly in neuronal development (Cruvinel et al. 2014). The loss of the S*NORD116* cluster has been associated with many clinical manifestations of Prader-Willi Syndrome. These clinical manifestations include psychosis, hypothalamic dysfunction, hyperphagia, developmental delay, and behavioral abnormalities. Because it is commonly lost in people living with Prader-Willi Syndrome, the *SNORD116* cluster has been identified as a crucial gene for upregulated expression in epigenetic treatment of Prader-Willi Syndrome (Salminen et al. 2020).

There is an area within the 15q11-q13 region that regulates the imprinting of these genes called the imprinting center (IC). The area that specifically regulates paternal imprinting is referred to as the PWS-IC because mutations in this area can lead to Prader-Willi Syndrome. PWS-IC contains an *SNRPN* promoter/exon 1 and has been shown to function as an activator of PEGs on the paternal allele. During gametogenesis in both males and females, the imprint on the chromosome is erased and redone so that each sex passes on the correct imprint. Active, unmethylated PWS-IC creates the paternal expressed genes during spermatogenesis. In males, the PWS-IC is activated so that it can prevent methylation of the paternally expressed genes on the paternal allele. In females, the PWS-IC is methylated, and thus, inactivated so that the paternally expressed genes are silenced on the maternal allele that will be passed on to the next generation. There are two possible strategies that the PWS-IC uses to activate paternal genes in the 15q11-q13 region. First, there could be a physical interaction between the PWS-IC and PEGs which protects them from methylation. Secondly, the genes downstream of PWS-IC could be expressed through a continuous transcript starting at the paternally active PWS-IC (Rabinovitz et al. 2012).

The imprinted genes involved in Prader-Willi Syndrome are expressed on the paternal allele and silenced on the maternal allele. This is done through epigenetic changes known as differential histone modification of the alleles. One study investigated the maternal silencing mechanism and found that Zinc-finger protein ZNF247 associates with histone methyltransferase to bind to and silence the maternal copies of

*Corresponding Author: **Zachary I. Merhavy**

the genes. In an induced pluripotent stem cell (iPCS) model of Prader-Willi Syndrome, the study found knockdown of the histone methyltransferase regulatory gene, *SETDB1*, results in decreased methylation of the PWS-IC on the maternal allele and partially restored expression of the maternal *SNORD116* cluster. Additionally, the study determined that the Zinc-finger ZNF247 was an epigenetic regulator of histone silencing, and disruption of its binding to histone methyltransferases could lead to reactivation and expression of previously silenced genes (Cruvinel et al. 2014).

Prader-Willi Syndrome can arise from three main mechanisms: a deletion in the paternal chromosome (70%), a maternal uniparental disomy (25-30%), in which the embryo contains two copies of the maternal chromosome, or an imprinting center defect (2-5%) (Gold et al. 2014).

Recent research has suggested that assisted reproductive techniques (ARTs), which are used to enhance fertility in humans, may be associated with DNA methylation errors that can lead to imprinting disorders. There was speculation that Prader-Willi Syndrome is one of these imprinting disorders (Pianka et al. 2018). When one study tried to find an association between Prader-Willi Syndrome and ARTs in a survey of 1,700 participants diagnosed with PWS, only 20 were conceived through ART. The study found that there is no association between ART and Prader-Willi Syndrome. However, it also found that within the group of 20, the frequency of maternal uniparental disomy was double compared to the total number of PWS participants. Because frequency of maternal uniparental disomy increases with maternal age, it is likely that the perceived association of PWS with ARTs may be because women who seek ART tend to be older, and thus, are more likely to have meiotic nondisjunction resulting in the uniparental disomy (Gold et al. 2014).

Current treatment for Prader-Willi is focused on preventing newborn failure to thrive, advancing behavioral improvement, and maintaining healthy weight. Infants with PWS typically exhibit feeding difficulties and special feeding techniques can help ensure proper nutrition. As children grow older, hyperphagia sets in, and restricting calories can prevent overeating and obesity. Once children reach pubescence, puberty can be corrected with hormone replacement therapy (Pianka et al. 2018). Growth hormone has been one of most widely used treatments for children with PWS. Studies have shown GH treatment to improve physical growth and muscle coordination as well as cognitive ability. Infants with PWS treated with GH scored higher in language, motor, and mental development tests when compared with untreated infants (Festen et al. 2008). These treatments are meant to mitigate symptoms for people living with Prader-Willi Syndrome and do not address the genetic causes of the condition.

Researchers are attempting to develop epigenetic-based therapies for Prader-Willi Syndrome to prevent the mutations, deletions, and imprinting mistakes in the 15q11-q13 region that result in its many different pathological phenotypes. Further research is required to fully understand the imprinting mechanism and the role of the lost genes involved in Prader-Willi Syndrome so that more effective treatments and therapies can be developed.

Angelman Syndrome

Angelman Syndrome (AS) is a congenital disease caused by defects in the genomic imprinting process. It exemplifies the difficulty of treating congenital diseases, as there is no known cure. The current approach is to attempt to alleviate the associated symptoms (Balaj et al. 2018). The prevalence of Angelman Syndrome is estimated to be between 1 in 12,000 to 1 in 20,0000 (Pianka et al. 2018). The wide variety of symptoms contributes to the difficulties of treating it. The disorder can be primarily classified as neurogenic (Balaj et al. 2018), which is specifically shown by the trademark happy demeanor associated with individuals affected by Angelman Syndrome. Developmental delay, hyperexcitability, insomnia, anxiety, microcephaly, intellectual disability, and severe speech impairment are some of the other complications associated with the neurogenic component (Balaj et al. 2018). Gastrointestinal dysfunction is another common complication of Angelman Syndrome. GERD, constipation, and cyclic vomiting have a high prevalence in these populations and proper treatment is needed to address these symptoms as well (Glassman et al. 2017).

The wide range of symptoms caused by Angelman Syndrome may be better understood through the complicated mechanisms responsible for causing the disease. Angelman Syndrome is the result of a mutation or deletion in the 15q11-q13 region on the maternal allele. The 15q11-q13 region contains ubiquitin ligase (*UBE3A*) which is no longer expressed as a result of this deletion or mutation. Unlike most genes that are simultaneously expressed by two alleles, *UBE3A* is silenced by paternal imprinting and defects in the maternal chromosome 15q11-q13 cannot be compensated (Kishino et al. 1997). There are currently four known mechanisms that cause Angelman Syndrome: "interstitial 15q11-q13 deletions (~80%), *UBE3A* mutations (~10%), paternal uniparental disomy (UPD) (~7%) and imprinting defect (~3%)" (Narayanan et al. 2019). *UBE3A* is an important gene for protein breakdown. It is used in many tissues throughout the body to regulate the amounts of varying types of proteins. A study on Drosophila indicated that a *UBE3A* equivalent gene that regulates monoamine synthesis, impacting concentrations of serotonin, may be implicated in Angelman Syndrome (Ferdousy et al. 2011). Dysfunction in regulation of serotonin levels may explain some complications like anxiety (Balaj et al. 2018), happy demeanor, insomnia, and even some of the gastrointestinal complications.

Complications associated with imprinting defects occur through microdeletions during gametogenesis of the Angelman Syndrome Short region of overlap (AS-SRO) and Prader-Willi Syndrome short region of overlap (PWS-SRO). These refer to the sequences of the deleted imprinting control regions AS-IC and PWS-IC in individuals who have Angelman Syndrome and Prader-Willi Syndrome respectively

*Corresponding Author: **Zachary I. Merhavy**

(Lewis et al. 2014). In more rare cases, defects in resetting the imprinted genes lead to Prader-Willi or Angelman Syndrome (Lewis et al. 2014). These two genes regulate each other's activity as a bipartite imprinting center, determining the methylation patterns on either the paternal or maternal chromosome 15 depending on the parent of origin. "The AS–SRO is an oocyte-specific promoter that generates transcripts that transit the PWS–SRO" (Lewis et al. 2014) The AS-IC serves to facilitate maternal gene expression by preventing methylation on the maternal allele initiated by the PWS-IC. As discussed above, the PWS-IC serves to activate the genes *MKRN3*, *MAGEL2*, and *SNRPN* (Lewis et al. 2014). In the case of Angelman Syndrome, the particular gene of interest is *SNRPN*, because it contains the *UBE3A-ATS* gene. Paternal expression of the *UBE3A-ATS* gene serves to silence the paternal expression of the *UBE3A* gene. Consequently, lack of expression of this gene on the maternal allele, facilitated by the AS-IC, ensures that proper imprinting has occurred and UBE3A is exclusively maternally expressed. "The absence of maternal *UBE3A–ATS* transcription on the maternal allele is necessary for *UBE3A* expression and the avoidance of AS." (Lewis et al. 2014). Microdeletions of AS-IC allow PWS-IC to activate gene *UBE3A-ATS* on the maternal allele (Meng et al. 2013), which in turn prevents expression of *UBE3A* and results in Angelman Syndrome. Further research is needed to understand the role of AS-IC in post-implantation epigenotype maintenance. The PWS-IC is important for regulating the maintenance of the imprinted gene since it will undergo rounds of methylation and demethylation at different stages of the embryos development (Haruta et al. 2005).

There is no known cure for Angelman Syndrome. The current treatment approach is to manage each set of symptoms individually. As discussed earlier, one potential cause of some of the behavioral problems associated with Angelman Syndrome is the GABAergic and serotonergic dysfunction. A case series found buspirone, an anti-anxiety medication, can reduce a number of the behavioral problems (Balaj et al. 2018). Despite the improvement on behavioral problems seen in this case series, it still has limited generalizability as it lacks a control group and only enrolled adult patients with deletion positive AS which may not be applicable to children who have different genotypes of Angelman Syndrome (Balaj et al. 2018). Additionally, many of the behavioral problems addressed by Buspirone through reduction of anxiety will not help the possible different triggers of that anxiety. Such triggers can include communication difficulty, gastro-intestinal problems, and insomnia. Buspirone may help reduce the problematic behaviors that arise from these symptoms, but these symptoms should be addressed themselves in order to make more significant improvements in quality of life for patients with Angelman Syndrome. Antiepileptic treatments are often necessary for patients with Angelman Syndrome. A recent study found that a low glycemic diet was a successful alternative to antiepileptic drug therapy (Grocott et al. 2017). Extensive all-inclusive treatments are fairly limited. Many studies have tried incorporating new methods like antibiotics, anti-inflammatory, or even drug therapies used for Parkinson's disease like levodopa (Ruiz-Antoran et al. 2018; Tan et al. 2018). These are just a few examples of the vast array of treatments that are being attempted or implemented. Thinking about all the things an individual with Angelman Syndrome and their family has to address quickly becomes overwhelming. Although continuing to research ways that can benefit individual symptoms in any way is important, a more focused vision forward through a more centralized treatment plan could dramatically improve the lives of those with Angelman Syndrome in the future.

One topic of interest that could lead to a more productive and centralized treatment of Angelman Syndrome is through gene therapy. Further research is needed in understanding the mechanism at the imprinting control region and ways to manipulate alternative gene expression in the case of interstitial deletion of the maternal chromosome 15. More specifically, a better understanding of the imprinting control regions could allow for manipulation of expression in individuals with Angelman Syndrome or Prader-Willi Syndrome. It is known that the PWS-SRO is important for resetting the methylation patterns throughout development (Haratu et al. 2005). Improved understanding of the AS-SRO could help facilitate a possible mechanism for manipulation of gene expression and provide an extremely effective therapy. Addressing congenital diseases at the root of their cause could provide broader improvement in quality of life.

Future Directions

As discussed above, the current therapeutic options for imprinting disorders such as AS and PWS are quite limited. Intervention strategies are focused on treating the symptoms, not the underlying genetic mechanism behind the disorders. This form of treatment can improve quality of life to some degree for many patients, but it is in no way curative. Patients and their caretakers are left with complex, expensive, time-consuming treatment options that must be continued throughout the patient's life. However, with the advent of new gene therapy technologies, there is a promising outlook for individuals affected by imprinting disorders. Since the diverse satellite of symptoms associated with imprinting disorders come from the silencing of a single allele, inducing expression of the silenced allele in early development would be an ideal solution. Gene therapies are ideal, because they fix the root of the problem, as opposed to treating the downstream effect. Additionally, resolving the genetic basis of the disorders would theoretically be a universal treatment for the vast array of symptoms associated with imprinting disorders.

Topoisomerase inhibitors provide one approach to restoring gene expression. In one study looking at Angelman treatment options, several topoisomerase inhibitors were found to induce *Ube3a* expression in *Ube3a*-null mice (Huang et al. 2012). Since Angelman syndrome is caused by errors in the maternal allele of *UBE3A* in neuronal cells plus a silent paternal copy of the allele, the idea behind this method is to unsilence the paternal copy. The paternal copy has the potential to be functionally normal, but it is dormant due to genetic silencing. Topoisomerase I inhibitor, Topotecan,

*Corresponding Author: **Zachary I. Merhavy**

appears to downregulate the *Ube3a* antisense transcript, which is responsible for repression of paternal *Ube3a* allele. Additionally, it was found that the paternal allele was catalytically active when unsilenced, indicating that it is indeed functionally normal once unsilenced. Restoring the normal paternal allele allows for proper expression of ubiquitin protein ligase enzyme coded by *Ube3a*. Topotecan is a chemotherapy drug approved for use in humans, so its effects in human patients are already well-characterized, making it an ideal drug to explore for use in Angelman Syndrome.

One treatment method currently being explored for Prader-Willi Syndrome focuses on reactivating the silenced maternal clusters SNRPN and SNORD116 that are implicated in the disorder (Kim et al. 2017). This study accomplished this by inactivating the enzyme that is responsible for the silencing, a histone methyltransferase (G9a), with inhibitors UNCO638 and UNCO642 proteins. The G9a inhibitors reduced the methylation of histones at the PWS-IC, increased expression of the SNRPN and SNORD116 clusters, and showed improved survival and growth in mice. Gene expression was successfully reinstated with the inhibition of the specific methyltransferase, suggesting that epigenetic-based therapy will provide a hopeful treatment route. However, there is substantial concern that using a methyltransferase inhibitor will alter expression of other genes. Methyltransferases are highly involved in genomic regulation universally, so the specificity of the inhibition would have to be extremely high in order to prevent the inhibition of structurally similar methyltransferases. If the selected methyltransferase inhibitor had an effect on multiple methyltransferases, this would cause inappropriate genetic regulation of the corresponding genes and undesirable offside effects. More work needs to be done to characterize these potential adverse effects and/or increase specificity before this therapy can be tested in humans.

Finally, another mechanism being explored is the use of adeno-associated virus (AAV) as a viral vector for delivery of DNA sequences to target cells. AAV therapy is becoming a mainstay in gene therapy. A transgene can be made with the AAV genome and the genetic material coding for a protein of interest. The host is then infected with the rAAV vector, and the genetic material is integrated into the host's genome for expression (National Institutes of Health, 2022). This could be useful for imprinting disorders because the AAV vector could be used to essentially replace the silenced gene into the patient, where it is incorporated into the genome, allowing for expression and restoration of genetic function. One study showed that this mechanism of gene replacement was proven to be an effective treatment for individuals with spinal muscular atrophy type 1. Spinal muscular atrophy type 1 is another neurological, single-gene disorder, so it is possible that a similar therapy could be effective for Angelman Syndrome and/or Prader-Willi Syndrome. A single infusion of the AAV containing the missing survival motor neuron 1 gene allowed for huge improvement in patients' condition and survival outcomes. This impressive result demonstrates the potential AAV-based gene replacement therapy could have in individuals with imprinting disorders. If an AAV could be used to deliver the silent gene, there would be potential for a curative effect. One challenge with this method is that levels of expression must be driven into the proper range, as overexpression of the silenced gene could cause other problems. Additionally, delivery must be optimized to drive expression for a prolonged period of time in the correct cell populations (Mendell et al. 2017). This therapy must be further researched and developed, but it provides a great deal of promise.

Early identification of imprinting disorders is also extremely important for developmental disorders (Zylka 2019). Unfortunately, many of the symptoms of imprinting disorders such as Angelman and Prader-Willi Syndrome are not apparent for the first few months or years of life, making it difficult to intervene early enough to prevent the harmful manifestations of the disease. In many imprinting disorders, such as Angelman and Prader-Willi Syndrome, the implicated genes play a crucial role in fetal development. There are several benefits to initiating treatment from birth or even prenatally, however early interventions require early diagnosis, hence the importance of fetal genetic testing. Studies done in animal models have shown that fetal gene therapy treatment of neurogenic diseases is more effective than neonatal treatment. One study showed that in a mouse model of Angelman Syndrome, reinstating the *Ube3a* allele with gene therapy in earlier developmental windows resulted in a better prognosis, with a decreased presentation of the neurological and motor deficits associated with Angelman Syndrome (Silva-Santos et al. 2015). This indicates that there are certain points in the development timeline at which treatment must be initiated in order for the individual to have the best prognosis. Additionally, fetal AAV gene replacement therapy has also been shown to be safer than the same treatment in adults due to the underdeveloped immune response in fetal life (Vandamme et al. 2017). The immune response has undesirable systemic effects and also decreases the efficacy of the treatment itself. Since prenatal treatment is so advantageous, there is a demand for accurate and safe prenatal genetic testing as well. There is some controversy over doing potentially dangerous genetic testing for a non-fatal disorder, such as Angelman and Prader-Willi Syndrome. Additionally, gaining access to the fetus for treatment is invasive and has potential dangers. On the other hand, in mild to severe cases, these disorders greatly impact quality of life for the affected individual and their caregiver, so the risks may be worth taking. Moving forward, early genetic testing and approval of fetal treatment maybe two of the biggest barriers to successful imprinting disorder therapy (Zylka 2019).

Conclusion

Imprinting disorders arise from a complex genetic mechanism resulting in the silencing of one parental allele. In this review, we discussed the genetic background and current treatment methods of Angelman Syndrome and Prader-Willi Syndrome, two common imprinting disorders. The current treatment options available for these disorders is limited and focused on

*Corresponding Author: **Zachary I. Merhavy**

mitigating the symptoms of the genetic abnormality. However, the rise of new gene therapies shows great promise as a future treatment option. Expanding the available gene therapies will also benefit other genetically based conditions, especially those caused by the alteration of a single allele. While there is still much work to be done, the fact that imprinting disorders result from the silencing of a single allele make them promising candidates for gene therapies such as topoisomerase inhibitors and AAV gene replacement therapy.

References

1. Balaj K., Walsh B., Mullet J., Palumbo ML., Thibert RL., McDougle CJ., & Keary CJ. (2019). Buspirone for the treatment of anxiety-related symptoms in Angelman syndrome: A case series. *PsychiatricGenetics,2*,51-56. doi:10.1097/YPG.0000000000000218
2. Cassidy SB., Schwartz S., Miller JL., & Driscoll DJ. (2012). Prader-Willi syndrome. *Genetics in Medicine, 14*(1), 10-26. doi:10.1038/gim.0b013e31822bead0
3. Crespi B., Read S., Salminen L., & Hurd P. (2018). A genetic locus for paranoia. *The Royal Society,14*(1). doi:10.1098/rsbl.2017.0694
4. Cruvinel E., Budinetz T., Germain N., Chamberlain S., Lalande M., & Martins-Taylor K. (2014). Reactivation of maternal SNORD116 cluster via SETDB1 knockdown in Prader-Willi syndrome iPSCs. *Human Molecular Genetics, 23*(17). doi:10.1093/hmg/ddu187
5. Eggermann T., Perez de Nanclares G., Maher ER., Temple IK., Tümer Z., Monk,D., … Netchine I. (2015). Imprinting disorders: A group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci. *Clinical Epigenetics, 7*(1). doi:10.1186/s13148-015-0143-8
6. Ferdousy F., Bodeen W., Summers K., Doherty O., Wright O., Elsisi N., Hilliard G., O'Donnell JM., & Reiter LT. (2011). Drosophila Ube3a regulates monoamine synthesis by increasing GTP cyclohydrolase I activity via a non-ubiquitin ligase mechanism. *Neurobiology of Disease, 41*(3), 669-677. doi:10.1016/j.nbd.2010.12.001.
7. Festen D., Wevers A., Lindgren B., Bohm B., & Otten J. (2007). Mental and motor development before and during growth hormone treatment in infants and toddlers with Prader–Willi syndrome. *Clinical Endocrinology, 68*(6). doi:10.1111/j.1365-2265.2007.03126.x
8. Girardot M., Feil R., & Llères D. (2013). Epigenetic deregulation of genomic imprinting in humans: Causal mechanisms and clinical implications. *Epigenomics, 5*(6), 715-728. doi:10.2217/epi.13.66
9. Glassman LW., Grocott OR., Kunz PA., Larson AM., Zella G., Ganguli K., & Thibert RL. (2017). Prevalence of gastrointestinal symptoms in Angelman syndrome. *American Journal of Medical Genetics, 173*(10), 2703-2709. doi:10.1002/ajmg.a.38401
10. Gold J. A., Ruth C., Osann K., Flodman P., McManus B., Lee HS., Donkervoort S., … Kimonis VE. (2014). Frequency of Prader-Willi syndrome in births conceived via assisted reproductive technology. *Genetics In Medicine, 16*(2), 164-169. doi:10.1038/gim.2013.97
11. Grocott OR., Herrington KS., Pfeifer HH., Thiele EA., & Thibert RL. (2017). Low glycemic index treatment for seizure control in Angelman syndrome: A case series from the center for dietary therapy of epilepsy at the Massachusetts General Hospital. *Epilepsy & Behavior, 68*(1), 45-50. doi:10.1016/j.yebeh.2016.12.018
12. Haruta M., Meguro M., Sakamoto Y., Hoshiya H., Kashiwagi A., Kaneko Y., … Oshimura M.(2005). Narrowed abrogation of the Angelman syndrome critical interval on human chromosome 15 does not interfere with epigenotype maintenance in somatic cells. *Journal of Human Genetics, 50*(1), 124-132. doi:10.1007/s10038-005-0231-2
13. Huang H., Allen JA., Mabb AM., King IF., Miriyala J., Taylor-Blake B., … Philpot BD. (2012). Topoisomerase inhibitors unsilence the dormant allele of Ube3a in neurons. *Nature, 481*(7380), 185. doi:10.1038/naturel0726
14. Kim Y., Lee H., Xiong Y., Sciaky N., Hulbert SW., Cao X., Everitt JI., Jin J., Roth B.L., & Jiang YH. (2017). Targeting the histone methyltransferase G9a activates imprinted genes and improves survival of a mouse model of Prader–Willi syndrome. *Nature Medicine, 23*(2), 213-222. doi:10.1038/nm.4257
15. Kishino T., Lalande M., & Wagstaff J. (1997). UBE3A/E6-AP mutations cause Angelman syndrome. *Nature Genetics, 15*(1), 70-73. doi:10.1038/ng0197-70
16. Lewis MW., Brant JO., Kramer JM., Moss JI., Yang TP., Hansen PJ., … Resnick JL. (2014). Angelman syndrome imprinting center encodes a transcriptional promoter. *Proceedings of the National Academy of Sciences USA, 112*(22), 6871-6875. doi:10.1073/pnas.1411261111
17. Margolis S., Sell G., Zbinden M., & Bird L. (2015). Angelman syndrome. *Neurotherapeutics, 12*(3), 641-650. doi:10.1007/s13311-015-0361-y
18. Mendell JR., Al-Zaidy S., Shell R., Arnold WD., Rodino-Klapac LR., Prior TW., … Burghes AHM. (2017). Single-dose gene-replacement therapy for spinal muscular atrophy. *The New England Journal of Medicine, 377*(18), 1713-1722. doi:10.1056/NEJMoa1706198
19. Meng L., Person RE., Huang W., Zhu PJ., Costa-Mattioli M., Beaudet AL. (2013). Truncation of Ube3a-ATS unsilences paternal Ube3a and ameliorates behavioral defects in the Angelman syndrome mouse model. *PLoS Genetics, 12*(9). doi:10.1371/journal.pgen.1004039

*Corresponding Author: **Zachary I. Merhavy**

20. Narayanan D., Ranganath P., Balakrishnan S., & Dalal A. (2019). Mosaic paternal uniparental isodisomy of 15q11-q13 region causing Angelman phenotype. *Clinical Dysmorphology, 28*(4),202-204. doi:10.1097/MCD.0000000000000284
21. National Institutes of Health – National Library of Medicine. (2022). How does gene therapy work? Retrieved from: https://ghr.nlm.nih.gov/primer/therapy/procedures
22. Pianka MA., McIntosh AT., Patel SD., Bakhshi PR., & Jung M. (2018). Close yet so far away: A look into the management strategies of genetic imprinting disorders. *American Journal of Stem Cells, 7*(4), 72-81.
23. Rabinovitz S., Kaufman Y., Ludwig G., Razin A., & Shemer R. (2012). Mechanisms of activation of the paternally expressed genes by the Prader-Willi imprinting center in the Prader-Willi/Angelman syndromes domains. *Proceedings of the National Academy of Sciences USA, 109*(19), 7403-7408. doi:10.1073/pnas.1116661109
24. Ruiz-Antoran B., Sancho-Lopez A., Cazorla-Calleja R., Lopez-Pajaro LF., Leiva A., Iglesias-Escalera G., … Avendano-Sola CA. (2018). A randomized placebo-controlled clinical trial to evaluate the efficacy and safety of minocycline in patients with Angelman syndrome (A-MANECE study). *Orphanet Journal of Rare Diseases, 13*(1), 144. doi:10.1186/s13023-018-0891-6
25. Salminen L., Read S., Hurd P., & Crespi B. (2020). Does SNORD116 mediate aspects of psychosis in Prader-Willi syndrome? Evidence from a non-clinical population. *Psychiatry Research, 268*. doi: 10.1016/j.psychres.2020.112858
26. Silva-Santos S., van Woerden GM., Bruinsma CF., Mientjes E., Jolfaei MA., Distel B., … Elgersma Y. (2015). Ube3a reinstatement identifies distinct developmental windows in a murine Angelman syndrome model. *Journal of Clinical Investigation, 125*(5), 2069-2076. doi:10.1172/JCI80554
27. Tan WH., Bird LM., Sadhwani A., Barbieri-Welge RL., Skinner SA., Horowitz LT., … Rufo P. (2018). A randomized controlled trial of levodopa in patients with Angelman syndrome. *American Journal of Medical Genetics, 176*(5), 1099-1107. doi:10.1002/ajmg.a.38457
28. Vandamme C., Adjali O., & Mingozzi F. (2017). Unraveling the complex story of immune responses to AAV vectors trial after trial. *Human Gene Therapy, 28*(11), 161-1074. doi:10.1089/hum.2017.150
29. Zylka MJ. (2020). Prenatal treatment path for Angelman syndrome and other neurodevelopmental disorders. *Autism Research, 13*(1), 11-17. doi:10.1002/aur.2203

*Corresponding Author: **Zachary I. Merhavy**