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Commentary

Comparative Genomic Studies in Angelman and Prader-Willi Syndromes

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DESCRIPTION

Angelman Syndrome (AS) and Prader-Willi Syndrome (PWS) are two distinct neurodevelopmental disorders caused by different disruptions in the same chromosomal region: 15q11-q13. Despite arising from genetic abnormalities in the same locus, AS and PWS display contrasting phenotypes due to a phenomenon known as genomic imprinting, where the expression of specific genes depends on their parental origin. Over the past decades, comparative genomic studies have deepened our understanding of the molecular basis of these syndromes, revealing the critical roles of imprinted genes and the mechanisms behind epigenetic regulation, uniparental disomy, and microdeletions.

PWS arises when genes that are normally paternally expressed in the 15q11-q13 region are either deleted or not expressed due to maternal uniparental disomy (both copies of chromosome 15 are inherited from the mother) or imprinting defects. In contrast, AS results from the absence of maternal expression of the *UBE3A* gene, typically due to maternal deletions, paternal uniparental disomy, mutations in *UBE3A*, or imprinting defects. While both disorders involve the same chromosomal region, the clinical manifestations and underlying genomic mechanisms are markedly different.

In PWS, the loss of paternal expression of genes such as *SNRPN*, *NDN*, and *MAGEL2* leads to a constellation of clinical features including neonatal hypotonia, feeding difficulties in infancy, hyperphagia leading to obesity in childhood, short stature, intellectual disability, hypogonadism, and behavioral issues such as temper outbursts and compulsivity. The *SNRPN* gene is especially important for its role in mRNA splicing and imprinting control in this region. Deletions in PWS typically span 5–6 megabases and include numerous imprinted and non-imprinted genes.

On the other hand, AS is primarily caused by the loss of function of the maternal allele of *UBE3A*, which encodes an ubiquitin-protein ligase involved in protein degradation in neurons. In neurons, only the maternal copy of *UBE3A* is active, while the paternal copy is silenced by an antisense transcript. Thus, any disruption to the maternal allele leads to an absence of functional UBE3A protein, resulting in the characteristic features of AS: Severe intellectual disability, speech impairment, seizures, ataxia, and a happy demeanor with frequent laughter and excitability. Like PWS, the most common genetic mechanism in AS is a deletion of the 15q11-q13 region on the maternal chromosome, but smaller mutations in the *UBE3A* gene or imprinting errors also contribute to the phenotype.

Comparative genomic analyses, using tools such as Fluorescence In Situ Hybridization (FISH), Methylation-Sensitive Multiplex Ligation-dependent Probe Amplification (MS-MLPA), and Next-Generation Sequencing (NGS), have allowed precise identification of the type and extent of deletions or mutations in the affected individuals. These studies have revealed that individuals with larger deletions tend to have more severe phenotypes in both AS and PWS. Furthermore, genotype-phenotype correlations have shown that those with uniparental disomy may present milder physical features but have increased risks for psychiatric or behavioral complications, particularly in PWS.

An important insight from these studies is the role of the Imprinting Center (IC), a small region that regulates the parent-of-origin-specific expression of genes in the 15q11-q13 region. Mutations or epigenetic defects in the IC can lead to both AS and PWS, depending on the parent of origin and the affected gene expression. For instance, a mutation in the maternal IC may prevent the activation of *UBE3A*, resulting in AS, whereas a mutation in the paternal IC may silence genes like *SNRPN*, leading to PWS.

Ongoing comparative studies have begun exploring how these genetic and epigenetic changes impact brain development and function using patient-derived stem cells and animal models. These models have helped identify disrupted pathways and potential therapeutic targets. For example, efforts are underway to reactivate the normally silent paternal copy of *UBE3A* in AS patients using antisense oligonucleotides. Similarly, understanding the role of *MAGEL2* and other genes in PWS has prompted research into targeted therapies for hyperphagia and behavioral issues.

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CONCLUSION

Angelman syndrome and Prader-Willi syndrome serve as powerful examples of how parent-of-origin effects and genomic imprinting can shape clinical outcomes from the same chromosomal region. Comparative genomic studies have illuminated the molecular underpinnings of these syndromes, particularly the roles of *UBE3A*, *SNRPN*, and the imprinting center. Continued research into the epigenetic regulation and gene-specific functions in this region holds promise for novel diagnostic tools and therapeutic interventions that can improve the lives of affected individuals.