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REVIEW

Emerging Gene and Small Molecule Therapies for the Neurodevelopmental Disorder Angelman Syndrome

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Abstract
Angelman syndrome (AS) is a rare (~1:15,000) neurodevelopmental disorder characterized by severe developmental delay and intellectual disability, impaired communication skills, and a high prevalence of seizures, sleep disturbances, ataxia, motor deficits, and microcephaly. AS is caused by loss-of-function of the maternally inherited *UBE3A* gene. *UBE3A* is located on chromosome 15q11–13 and is biallelically expressed throughout the body but only maternally expressed in the brain due to an RNA antisense transcript that silences the paternal copy. There is currently no cure for AS, but advancements in small molecule drugs and gene therapies offer a promising approach for the treatment of the disorder. Here, we review AS and how loss-of-function of the maternal *UBE3A* contributes to the disorder. We also discuss the strengths and limitations of current animal models of AS. Furthermore, we examine potential small molecule drug and gene therapies for the treatment of AS and associated challenges faced by the therapeutic design. Finally, gene therapy offers the opportunity for precision medicine in AS and advancements in the treatment of this disorder can serve as a foundation for other single-gene neurodevelopmental disorders.

Keywords Angelman syndrome · Seizures · Gene therapy · Animal models · Antisense oligonucleotides · Stem cells · Precision medicine · Delivery · Preclinical · Small molecules · Pharmacology · Treatment

Introduction

Angelman syndrome (AS) is a rare (~1:15,000) neurodevelopmental disorder characterized by severe developmental delay and intellectual disability, impaired communication skills, and a high prevalence of seizures, sleep disturbances, ataxia, and motor deficits [1, 2]. AS is generally diagnosed in patients over the age of one, as its behavioral characteristics become more readily pronounced and distinct compared to other developmental disorders [3]. Seizures are highly prevalent in AS and occur in over 80% of the population [4]. Seizures typically start early in life and are often (~ 1/3) resistant to classic antiepileptic drugs. They continue throughout an individual's lifetime and present across multiple seizure types including, but not limited to, absence, myoclonic, and generalized clonic-tonic seizures [5, 6]. Given their frequency and treatment resistance, seizures in AS contribute to significantly higher burden of care [7]. Currently, there is no cure for AS and the only treatments available are those designed to temporarily mitigate symptoms throughout a patient's lifetime.

AS is caused by loss-of-function of the maternally inherited *UBE3A* gene [8–11]. *UBE3A* is located on chromosome 15q11–13 and is biallelically expressed throughout the body but only maternally expressed in the brain due to imprinting [12–14]. The paternal copy is silenced by a long (> 600 kb) non-coding RNA antisense transcript referred to as the *UBE3A*-ATS [15–17]. Several genetic etiologies lead to AS including de novo interstitial deletions of the maternal allele (~ 65–70% of the AS population), loss-of-function mutations in the maternal allele (5–11%), uniparental disomy resulting in two normal functioning paternal alleles (3–7%), and various imprinting defects (3%) [18–20].

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