Neurotherapeutics (2015) 12:641–650
DOI 10.1007/s13311-015-0361-y

REVIEW

Angelman Syndrome

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Published online: 4 June 2015
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Abstract In this review we summarize the clinical and genetic aspects of Angelman syndrome (AS), its molecular and cellular underpinnings, and current treatment strategies. AS is a neurodevelopmental disorder characterized by severe cognitive disability, motor dysfunction, speech impairment, hyperactivity, and frequent seizures. AS is caused by disruption of the maternally expressed and paternally imprinted *UBE3A*, which encodes an E3 ubiquitin ligase. Four mechanisms that render the maternally inherited *UBE3A* nonfunctional are recognized, the most common of which is deletion of the maternal chromosomal region 15q11-q13. Remarkably, duplication of the same chromosomal region is one of the few characterized persistent genetic abnormalities associated with autistic spectrum disorder, occurring in >1–2 % of all cases of autism spectrum disorder. While the overall morphology of the brain and connectivity of neural projections appear largely normal in AS mouse models, major functional defects are detected at the level of context-dependent learning, as well as impaired maturation of hippocampal and neocortical circuits. While these findings demonstrate a crucial role for ubiquitin protein ligase E3A in synaptic development, the mechanisms by which deficiency of ubiquitin protein ligase E3A leads to AS pathophysiology in humans remain poorly understood. However, recent efforts have shown promise in restoring functions disrupted in AS mice, renewing hope that an effective treatment strategy can be found.

Key Words Angelman syndrome · neurodevelopmental disorders · autism · ubiquitin ligase · Ube3a · Imprinting.

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Clinical Overview

In 1965, the English physician Harry Angelman described 3 patients who presented with a stiff, jerky gait, absence of speech, excessive laughter, and seizures. The disorder that came to bear his name [Angelman syndrome (AS)] is now recognized to affect approximately 1 in 15,000 individuals and is characterized by motor dysfunction, severe intellectual disability, speech impairment, seizures, hyperactivity, and autism spectrum disorder (ASD) as a common comorbidity [1].

Developmental delay in individuals with AS is usually observed within the first year of life. Though most individuals lack speech entirely, some who are mildly affected can acquire a few words. Receptive language is less impaired. Seizures occur in >80 % of patients, and onset is usually before the age of 3 years. Movement disorders include tremors, jerkiness, and ataxia. The characteristic behaviors of AS include mouthing of objects, happy demeanor with easily provoked laughter, attraction to water, hyperactivity, short attention span, and decreased sleeping (see recent reviews for more detailed description of the clinical phenotype [2–4]). These features of AS can be seen in other neurodevelopmental disorders, leading to a broad differential diagnosis [5], which has recently been reviewed (Table 1) [6]. Overlapping clinical features may indicate common neurophysiological pathways,

Table 1 Overlap of clinical features between various neurodevelopmental disorders

	Seizures	Speech impairment	Ataxia or broad based gait±arms upheld	Hypotonia	Happy disposition; easily provoked laughter	Microcephaly	Hyperactivity	Short attention span	Sleep disturbance	Infant feeding difficulties	Drooling	Mouthing	Stereotypy	Abnormal MRI
AS	+	+	+	+	+	+	+	+	+	+	+	+	+/−	CC/DM
PHS (*TCF4*)	+	+	+	+	+								+	PF
CS (*SLC9A6*)	+	+	+		+	+					+			PF
RS (*MECP2*)	+	+	+			+							+	
ATRX	+	+		+	+	+					+			
ASL defic.	+	+	+		+/−	+							+	PF
MWS (*ZEB2*)	+	+	+	+	+	+						+		+/−
2q23.1-(*MBD5*)	+		+			+		+						
KdVS (*KANSL1*)	+			+	+	−				+				
KS (*EHMT1*)	+			+					+					
FOXG1 defic.	+			+		+			+					CC
PMS(22q13-)	+			+			+	+		+		+		PF
CDKL5defic.	+			+					+					
HERC2 defic.	+/−			+	−			+						

	Prognathism	Broad mouth	Ear dysmorphism	Genital anomalies	Congenital heart defect	Males only	Females only	Regression	Apathy/ catatonia	Hyperventilation/ apnea	Limited purposeful hand use	Hirschsprung
AS	+	+										
PHS (*TCF4*)		+	+							+		+/−
CS (*SLC9A6*)						+		+				
RS (*MECP2*)							+	+		+	+	
ATRX				+	+	+						
ASL defic.												
MWS (*ZEB2*)	+	+	+	+	+							+
2q23.1-(*MBD5*)												
KdVS (*KANSL1*)				+								
KS (*EHMT1*)	+			+	+				+			
FOXG1 defic.												
PMS(22q13-)												
CDKL5defic.												
HERC2 defic.												

MRI = magnetic resonance imaging; AS = Angelman syndrome; CC = corpus callosum hypoplasia; DM = delayed myelination; PHS = Pitt–Hopkins syndrome; PF = posterior fossa abnormalities; CS = Christianson syndrome; RS = Rett syndrome; ATRX = alpha-thalassemia X-linked mental retardation; ASL = adenyl succinate lyase; defic. = deficiency; MWS = Mowat–Wilson syndrome; KdVS = Koolen de Vries syndrome; KS = Kleefstra syndrome; PMS = Phelan–McDermid syndrome

most of which remain to be elucidated. The diagnosis of AS should be confirmed molecularly, as discussed below, in order to provide accurate information regarding prognosis, complications, and risk of recurrence. Precision in diagnosis helps to inform future research endeavors by establishing the genotype–phenotype relationship more clearly and providing a foundation upon which the success of new therapies can be gauged.

Genetic Etiology and Diagnosis

Human genetic studies revealed that AS is caused by 4 molecular mechanisms: *de novo* maternal deletions of chromosome 15q11-q13 (70–80 %); intragenic mutations in the maternally inherited *UBE3A* within chromosome15q11-q13 (10–20 %); paternal uniparental disomy (UPD) for chromosome 15q11-q13 (3–5 %); or imprinting defects within chromosome 15q11-q13 that alter the expression of maternally inherited *UBE3A* (3–5 %) (Fig. 1) [7]. While there is variability with each molecular class of AS, in general those with deletion have a more severe phenotype, and those with UPD and imprinting defects a less severe phenotype [2, 8–11].

The diagnostic algorithm described in Fig. 2 begins with testing to determine the DNA methylation status of chromosome 15q11-q13, not specifically *UBE3A*. A methylation pattern showing only the paternal imprinting pattern secures the diagnosis of AS, and further testing is needed to distinguish between deletion, UPD or an imprinting defect as the etiology. Fluorescent *in situ* hybridization determines if a deletion has occurred. Chromosomal microarray can further refine the deletion size, which has been shown to correlate with severity of clinical features [8, 11, 12]. For those whom deletion is excluded by fluorescent *in situ* hybridization, DNA marker analysis of the proband's and parents' chromosome 15q11-q13 region will confirm or exclude UPD. When both UPD and 15q11-q13 deletion have been excluded in an individual with abnormal DNA methylation, AS is therefore due to an imprinting defect, most of which are epigenetic phenomena, and a minority of which are caused by small imprinting center

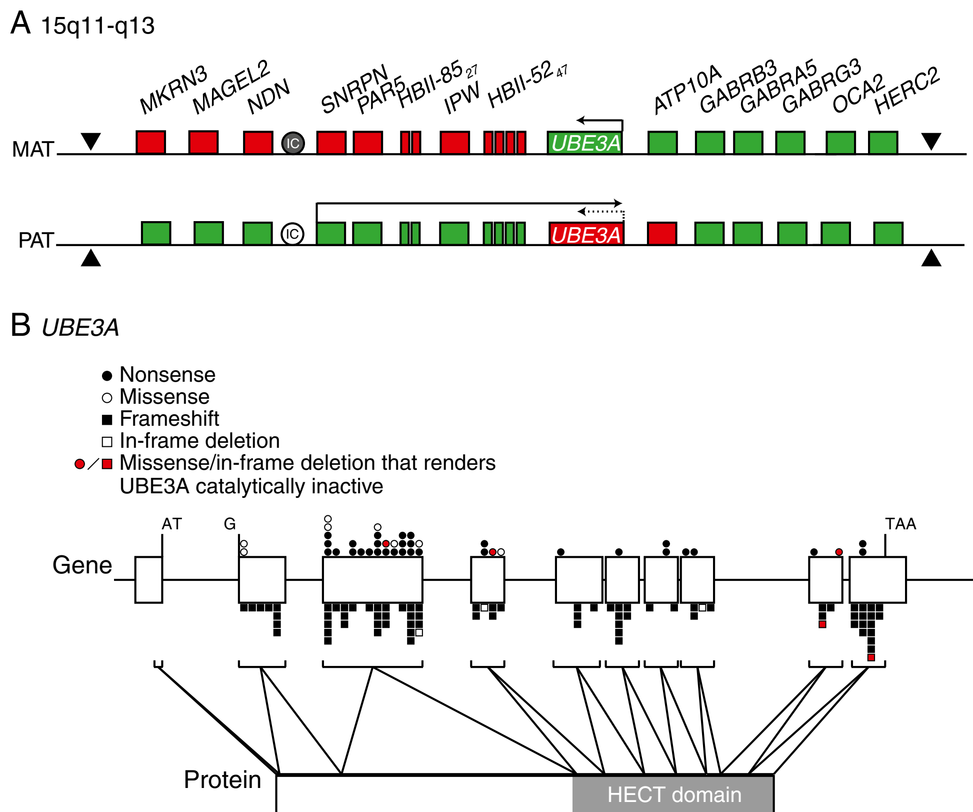

Fig. 1 Organization of Chr15q11-q13 and schematic of *UBE3A* clinical mutations. (A) Diagram of maternal (MAT; top) and paternal (PAT; bottom) regions of human chromosome 15q11-q13. Green boxes represent actively expressed genes, while those whose expression have been silenced through genomic imprinting (maternal allele) or through expression of the antisense transcript [paternal ubiquitin protein ligase E3A (UBE3A)] are represented by red boxes. Active and inactive imprinting centers (IC) are represented by gray and white filled circles, respectively. Black triangles represent low copy number repeats that mediate deletions in the region. (B) Schematic of human *UBE3A* isoform 1 mapped with clinical mutations found in patients with Angelman syndrome. Exons (boxes) and intronic sequences (lines) are approximately to scale. The last 350 residues of UBE3A constitute its functional domain, the HECT (homologous to the E6-AP carboxyl terminus) ubiquitin ligase domain

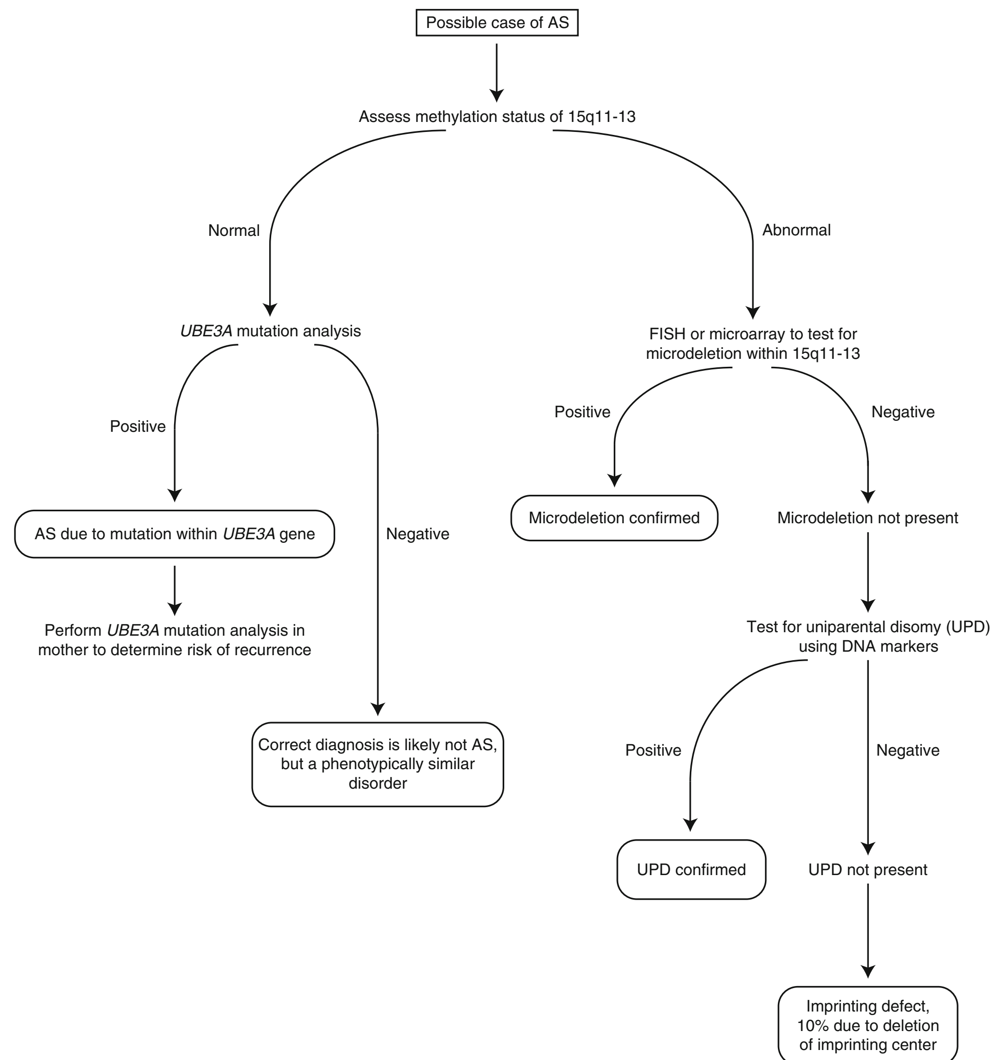

Fig. 2 Angelman syndrome (AS) diagnostic algorithm. FISH = fluorescent *in situ* hybridization

deletions or point mutations (testing for the latter is available on research basis). Abnormal DNA methylation is observed in 80–90 % of cases of AS. The remaining cases, which show a normal pattern of DNA methylation, are due to *UBE3A* point mutations or small intragenic rearrangements. *UBE3A* sequencing that returns normal excludes point mutations, but small deletions within *UBE3A* require multiplex ligation-dependent probe amplification for detection [13]. While it was formerly believed that 10–15 % of cases of AS were due to an as-yet-unrecognized molecular etiology, it is more likely that these patients represent phenocopies and actually have other diagnoses, such as those listed in Table 1 [2, 6].

Within human chromosomal region 15q11-q13 there are maternally imprinted (i.e., paternally expressed) genes, paternally imprinted (i.e., maternally expressed) genes, and biallelically expressed genes (Fig. 1A). Mouse studies have shown *Ube3a* to be paternally imprinted in the brain and biallelically expressed in all other tissues that have been examined [14]. This brain-specific imprinting of *UBE3A* is presumably found in humans as well [15, 16]. Moreover, within the brain there appears to be some regional or tissue-specific developmental control of *Ube3a* imprinting in neurons and restriction of imprinting to neurons (and not glia) in the central nervous system [17]. The mechanism of this brain region-specific imprinting of *Ube3a* has just begun to be explored (as reviewed in [18, 19]). Recent evidence indicates that an antisense RNA transcript (ATS), *Ube3a-ATS*, is necessary for this brain-specific imprinting of *Ube3a* [20, 21]. Greater understanding of this imprinting mechanism is likely to provide important insight into new approaches for treating AS (see below).

Patients with AS harboring a deletion of the maternal copy of chromosome 15q11-q13 presumably display normal expression of the maternally imprinted genes from the normal paternal chromosome, very little *UBE3A* expression (in the brain), and hemizygous expression of genes that are typically expressed from both chromosomes. Patients with AS with UPD and imprinting defects are predicted to have elevated

expression of the maternally imprinted genes and very little expression of *UBE3A*. Those harboring loss-of-function mutations in *UBE3A* presumably have normal expression of all other genes in the region and very little or defective ubiquitin protein ligase E3A (UBE3A) protein in the brain. While the commonality between these genetic etiologies is a loss of UBE3A activity, patients with AS due to a chromosomal deletion present with more severe phenotypes than those with AS due to other molecular etiologies [9, 10, 22, 23]. One possibility is that the other genes located within 15q11-q13 play significant roles in brain development. Insight into this comes from studies associating this chromosomal region, and possibly *UBE3A*, with ASD [24, 25].

AS and Autism

ASD is a complex neurological disorder characterized by impairment in social interactions and language/communication skills in combination with rigid, repetitive behaviors. Despite the high prevalence of ASD (recent reports indicate that as many as 1 in 68 children are born with ASD), a specific etiology is identified in <20 % of patients (as reviewed in [26]). Notwithstanding, there is a significant genetic component to ASD, as illustrated by the observation that 1) risk of recurrence is approximately 20 % for siblings, and 2) concordance for autism in monozygotic twins is 8 times higher than in dizygotic twins [27–31]. For this reason, considerable effort has been invested into identifying human genetic causes of ASD. Genetic abnormalities within chromosomal region 15q11-q13 are among the most prevalent of all mutations identified in ASD, accounting for approximately 1–2 % of all cases [32, 33]. Furthermore, recent reports indicate that copy number variants of 15q11-q13 are associated with autism [34]. These data, together with the observation that individuals with AS often have a comorbid diagnosis of autism, suggest that mutation of *UBE3A* may play a role in the etiology of ASD. However, it remains to be determined whether changes in *UBE3A* expression itself are sufficient to cause autism.

AS Mouse Models

Mouse models generated by targeted inactivation of *Ube3a* provide additional support to the causative role of *UBE3A* mutations in AS [35, 36]. Upon inheritance of *Ube3a* deletion through the maternal but not the paternal germline, mice recapitulate many features of the human disorder, displaying impaired motor function, seizures, and deficits in context-dependent and spatial learning (summarized in Table 2 and discussed below). The observation that paternal imprinting of *Ube3a* occurs in mature neurons, but not in immature neurons, glia or non-nervous system tissues, reinforces the idea that the loss of UBE3A function in the central nervous system underlies AS pathology [14, 17, 35, 36, 45].

Maternal (and not paternal) deletion of *Ube3a* (referred to as *Ube3a*$^{m-/p+}$) mediates the behavioral phenotypes. For the mouse models of AS caused by *Ube3a* maternal deletions, there is some phenotypic inconsistency, after accounting for genotype and background strain [38]. Motor deficits on rotarod and beam balance tests have been seen consistently [25, 35, 36, 38, 39]. Differences in gait analysis, clasping, pole test, and tape removal are less consistently reported [40]. Hypoactivity has been shown in the *Ube3a*$^{m-/p+}$ animals both in an open field type of environment, reflected in slower speed and less distance travelled, and in water-maze testing, where slower swim speed is observed [38]. Generally, *Ube3a*$^{m-/p+}$ mice show decreased freezing in contextual fear conditioning and no deficit in cued fear conditioning, although the opposite has also been reported [35, 36, 38]. Depending on the strain and reporting laboratory, *Ube3a*$^{m-/p+}$ mice may show a deficit in water-maze acquisition, testing, or reversal training [35, 36, 38, 42]. Anxiety phenotypes are reported, as shown by dark preferences in light–dark tests and lack of novel object preference, as well as preference for edges and increased freezing in open field-testing [38, 43]. Mice with AS bury fewer marbles than their wild-type controls [38]. This robust and reproducible decrease in marble burying exhibited by mice with AS may indicate abnormal repetitive, compulsive, anxiety-driven behaviors, or motor dysfunction [46]. Socially, *Ube3a*$^{m-/p+}$ mice show reduced activity in social testing but not substantial social preference deficit [25, 38]. Finally, *Ube3a*$^{m-/p+}$ animals show pathway-specific misregulation of dopaminergic release, potentially contributing to both reward and motor phenotypes in these animals, and informing clinical trials for levodopa and the use of stimulants in patients with AS [44]. These animals are also prone to seizures depending on the background strain [35].

While many studies have focused on AS mouse models that only remove the maternal *Ube3a*, one group also worked toward generating a mouse model with a larger maternal deletion of mouse chromosome 7 that mirrors the human maternal deletion of chromosome 15q11-q13. Many of the phenotypes observed in this AS mouse model are the same as maternal deletion of *Ube3a* only: impaired rotarod performance, contextual fear conditioning deficit, water-maze deficits, communication deficits as measured by abnormal newborn isolation-induced ultrasonic vocalizations, seizures, and light–dark activity alterations [37]. These data are consistent with the loss of *UBE3A* playing a significant role in AS etiology.

Several studies using mouse models duplicated for a portion of mouse chromosome 7 syntenic to the human chromosomal region 15q11-q13 indicate that an increase in *Ube3a* expression leads to mild but significant changes in neuronal

Table 2 Comparison of phenotypes in Angelman syndrome and autism mouse models with mutations in *Ube3a* or deletions of mouse chromosome 7 (paralog of human chromosome 15q11-q13)

Behavior	$Ube3a^{m-/p+}$(129)	*Ube3a*$^{m-/p+}$(C57)	Maternal deletion*	Ube3a triplication†	Maternal duplication‡	Paternal duplication§	References
Seizures	+		+				[35, 37]
Rotarod	+	+/−	+	−	−	+	[24, 25, 35–39]
Beam balance	+	+					[35, 36, 39]
Gait		+					[39–41]
Clasping		+					[40]
Pole test		+					[40]
Tape removal		+					[40]
Context fear conditioning	+	+/−	+		−	−	[24, 35–38]
Cued fear conditioning	−	+	−		−	+	[24, 35, 37, 38]
Morris water maze	+	+	+			+	[24, 35–38, 42]
Barnes maze					−	+	[24]
Novel object recognition		+		−			[25, 43]
Light–dark test		+	+		−	−	[24, 37, 43]
Open field		+	−	−	−	−	[24, 25, 37, 38, 43]
Marble burying		+					[38]
Hypoactivity	+	+					[38]
Elevated plus maze				−	−	+	[24, 25]
Forced swim test					−	+	[24]
Social testing		+/−		+	−	+	[24, 25, 38]
Cocaine reward		+					[44]
USV			↑pup	↓adult	−	↓adult	[24, 25, 37]

A "+" indicates abnormal behavior; "−" indicates normal behavior; "+/−" indicates confounding results; empty spaces indicate behaviour has not been tested

Ube3a$^{m-/p+}$ mutant mice described in [35] and [36] (129 and C57 indicated mouse background strain. Not all indications in the table are of pure background. See individual references for details of mouse generation)

USV = ultrasonic vocalization

*Maternal deletion described in [37]

† Ube3a triplication described in [25]

‡ Maternal duplication described in [24]

§ Paternal duplication described in [24] and [41]

function. Duplication of this chromosomal region specifically on the maternal allele leads to increased *Ube3a* expression with little effect on animal behavior [24], whereas the corresponding paternal duplication leads to alterations in behavior consistent with autism [24, 41]. An inconsistency between these 2 studies is that while relative levels of *Ube3a* mRNA are unchanged in the paternal duplication of this chromosomal region as expected, Ube3a protein level is unexpectedly elevated, suggesting that elevated Ube3a levels contribute to the observed phenotypes in these studies. Consistent with this, using a bacterial artificial chromosome recombination approach, mice harboring extra copies of only *Ube3a* exhibit impaired social behavior, decreased communication as measured by interaction-induced adult ultrasonic vocalizations (number and duration during males response to female urine and same sex pairs), and increased repetitive behavior as measured by increased grooming time [25]. These animals do not exhibit anxiety, motor, memory, or sensory behavioral deficits. These studies imply that elevated UBE3A alone in patients with autism may be sufficient to give rise to several core autism-related behaviors. Continued efforts to understand the mechanistic pathways downstream of Ube3a will provide new insights into our understanding of how alterations in the cellular abundance of Ube3a protein may lead to neurological disorders related to autism.

Cellular and Molecular Underpinnings of AS

Despite the critical role that UBE3A plays in human cognitive function, relatively little is known about UBE3A's role in human nervous system development or how the perturbation of

UBE3A expression leads to the cognitive and language impairment underlying AS and ASD. The development of *Ube3a*-deficient mice has been especially useful for investigating the molecular and cellular events contributing to the pathophysiology of AS. As detailed above, *Ube3a*-deficient mice display phenotypes that correlate well with the human disorder, including impaired learning and memory, motor deficits, and seizures [35]. While the overall morphology of the brain and connectivity of neural projections appears largely normal in *Ube3a*-deficient mice, defects are detected at the level of synapses. *Ube3a*-deficient mouse brains exhibit reduced density of dendritic spines (the location of >95 % of excitatory synapses) in both hippocampal and neocortical neurons [47, 48]. Consistent with Ube3a playing an important role in synaptic function, electrophysiological experiments have demonstrated that long-term potentiation and long-term depression are impaired in the hippocampus and neocortex of mice with AS [35, 42, 47, 49, 50]. Additionally, studies implicate Ube3a in experience-dependent visual cortical plasticity [47]. Other studies have found that deletion of *Ube3a* also leads to changes in inhibitory synapse function [51]. These findings suggest the intriguing hypothesis that AS may result from a fundamental defect in excitatory synapse development leading to lower numbers of functional excitatory and inhibitory synapses in the brain. While these experiments demonstrate a crucial role for *Ube3a* in synaptic transmission and suggest that the fundamental defect may be in synaptic function, the mechanisms by which Ube3a regulates synaptic function remain to be elucidated.

UBE3A encodes a HECT (homologous to the E6-AP carboxyl terminus) domain E3 ubiquitin ligase that catalyzes the addition of ubiquitin to lysine residues on substrate proteins, leading to the degradation of the ubiquitinated substrate protein [52–59]. Human genetic studies have identified several mutations that specifically disrupt the ubiquitin ligase activity of UBE3A while having no effect on protein expression or substrate interactions (Fig. 1) [60]. Given that the ligase activity is important for the ubiquitination and degradation of target proteins, these observations suggest that disruption of UBE3A activity leads to inappropriately high levels of these target proteins and consequent neuronal dysfunction. While several candidate substrates have been discovered, AS-relevant targets leading to neural defects after UBE3A loss have yet to be identified [61, 62]. In addition, because *UBE3A* lies within a region of chromosome 15 that is duplicated in a subset of heterogeneous ASDs, it remains possible that altered levels of UBE3A substrates might be a mechanism relevant to the etiology of autism [34, 63].

Although the causative role for *UBE3A* mutations in AS has been appreciated since 1997, to date, no approach has been effective in significantly advancing our understanding of the molecular substrates of UBE3A relevant to synaptic dysfunction and disease etiology. Recent studies using *Drosophila melanogaster* have identified potential fly Dube3a substrates [64]. In an attempt to take an unbiased approach to identify AS-relevant substrates of Ube3a, several laboratories have tried to compare the complement of ubiquitinated proteins in AS mouse brains with wild-type brains using quantitative mass spectrometry [52, 62, 65]. It is unclear from the results of these studies which substrates are affected directly or indirectly by Ube3a. More importantly, these studies have yet to evaluate the relevance of the identified substrates to the development of AS phenotypes. Such molecular studies are vital to our understanding of the mechanisms by which UBE3A functions. Future studies investigating the relevance of the discovered UBE3A substrates to the development of AS may shed light on the molecular pathogenesis of other neurodevelopmental disorders, such as ASDs.

Treatment

Current

At present, there is no specific treatment for AS. Treatment is supportive and includes 1) therapies to mitigate gross and fine motor delays; 2) augmentative communication strategies such as the use of communication devices, picture exchange cards, and modified sign language; and 3) intervention for comorbid ASD when present [2–4, 8–10]. The remainder of treatment is limited to managing the problems associated with AS [66]. Gastrointestinal problems such as gastroesophageal reflux disease and constipation are managed with pharmacological agents when dietary modifications are insufficient. Sleep problems are treated with a combination of pharmacologic and behavioral interventions. Seizures are treated with anticonvulsants (valproic acid, clonazepam, lamotrigine and levetiracetam have greatest efficacy) and, rarely, ketogenic diet and vagal nerve stimulation are needed for seizures refractory to pharmacological intervention [67]. Those with substantial hypopigmentation require skin and eye protection. Disruptive behaviors can usually be managed with a behavior modification program but the occasional patient with AS will require medications for aggressive behavior. Longitudinal care includes monitoring for scoliosis and anticipatory guidance regarding obesity (more common in the nondeletion group) [see also [2–4] (and the other citations in the second paragraph of "Clinical Overview") for more detailed descriptions of clinical features and management].

Research and Development

Several clinical trials conducted thus far have produced negative results. Attempts to alter methylation of *UBE3A* using promethylation vitamin supplements to increase transcription from the paternal allele did not alter the phenotype of AS [68,

69]. Data analysis is in progress for a randomized, placebo-controlled trial using levodopa/carbidopa to treat AS (ClinicalTrials.gov identifier: NCT01281475). The rationale for this trial was based on the observations that levodopa influenced phosphorylation of calcium/calmodulin-dependent protein kinase II threonine residues in a rat model of Parkinson's disease [70, 71]; the finding of dopaminergic neuronal loss in AS mouse models [40]; and a report of 2 adults with AS and Parkinsonian symptoms who responded to levodopa [72]. Results of a short open-label trial of minocycline treatment (ClinicalTrials.gov identifier: NCT01531582) were recently published and suggest that small benefits could be possible [73].

Encouraging preclinical studies suggest that new avenues for treatment could open up in the near future. Several groups have attempted to reactivate the silenced paternal copy of *Ube3a* [74–76]. Large-scale small compound screening led to identification of the topoisomerase inhibitor topotecan as having the potential to activate *Ube3a* from the paternal allele [74, 76, 77]. While details of topotecan's action remain to be elucidated, recent studies suggest that topotecan works by reducing the levels of *Ube3a*-ATS, thereby unsilencing the paternal allele of *Ube3a*. This may be accomplished through inhibition of topoisomerases, which relieves the torsional stress that results from the transcription of large transcripts thus blocking the production of the *Ube3a*-ATS or by stabilizing R-loops, or RNA–DNA hybrids, resulting in chromatin decondensation and *Ube3a*-ATS silencing [76, 77]. Another approach used antisense oligonucleotides to interfere with the *Ube3a*-ATS transcript, which mediates the silencing of the paternal allele [75]. While some phenotypes were rescued by this approach in adulthood, including contextual fear testing, many were not, indicating that this restoration of Ube3A protein is insufficient for full rescue, owing to the developmental timing, protein level, or some other factor. However, this approach was effective in adult mice, suggesting that reactivation of *Ube3a* can reverse some behavioral deficits, even after several months of development with a defective copy of *Ube3a*. Whether the specificity of the antisense oligonucleotides for the target transcript limits systemic toxicity in humans remains to be tested. Drug delivery and blood–brain barrier considerations will be additional challenges to overcome. Alternative efforts to target key disrupted pathways in these AS mice, such as those mediated by calcium/calmodulin-dependent protein kinase II, Na/K-adenosine triphosphatase, activity-regulated cytoskeleton-associated protein and neuregulin-ErB4, for example, have met with some success in rescuing various phenotypes observed in mice with AS [42, 49, 50, 78]. Rescuing AS phenotypes through manipulation of Ube3a substrates have not yet been tested rigorously.

Conclusion

Loss of maternal Ube3a is a known cause of AS. While many deficits in neurons are known from the mouse model of AS the molecular pathophysiology in humans is poorly understood. An improved understanding will be vital to developing effective treatment approaches for AS. Given the apparent symptomatic overlap of AS with other neurodevelopmental disorders, including ASD, efforts towards understanding and treating AS are anticipated to be broadly applicable.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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