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### Authors

Cassater, Daiana

Bustamante, Mariana

Sach-Peltason, Lisa

et al.

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## Clinical characterization of epilepsy in children with Angelman syndrome

**Daiana Cassater<sup>1</sup>, Mariana Bustamante<sup>2</sup>, Lisa Sach-Peltason<sup>2</sup>, Alexander Rotenberg<sup>3</sup>, Mark Nespeca<sup>4</sup>, Wen-Hann Tan<sup>5</sup>, Lynne M. Bird<sup>4</sup>, Joerg F. Hipp<sup>6,\*</sup>**

<sup>1</sup>Roche Pharma Product Development, Immunology, Infectious Diseases and Ophthalmology (I2O), F. Hoffmann–La Roche Ltd., Switzerland

<sup>2</sup>Roche Pharma Research and Early Development, pRED Informatics, Roche Innovation Center Basel, F. Hoffmann–La Roche Ltd., Switzerland

<sup>3</sup>Department of Neurology, Boston Children's Hospital; Harvard Medical School, Boston, Massachusetts, USA

<sup>4</sup>Department of Pediatrics, University of California, San Diego; Genetics / Dysmorphology, Rady Children's Hospital San Diego, California, USA

<sup>5</sup>Division of Genetics and Genomics, Boston Children's Hospital; Harvard Medical School, Boston, Massachusetts, USA.

<sup>6</sup>Roche Pharma Research and Early Development, Neuroscience and Rare Diseases, Roche Innovation Center Basel, F. Hoffmann–La Roche Ltd., Switzerland

### Abstract

**Background:** Epilepsy is highly prevalent in children with Angelman syndrome (AS) and its detailed characterization and relationship to the genotype (deletion vs non-deletion) is important both for medical practice and for clinical trial design.

**Methods and materials:** We retrospectively analyzed the main clinical features of epilepsy in 265 children with AS who were enrolled in the AS Natural History Study (ASNHS), a multicenter,

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\* **Corresponding author:** Joerg F. Hipp, Roche Pharma Research and Early Development, Neuroscience, Ophthalmology and Rare Diseases, Roche Innovation Center Basel, Grenzacherstrasse 124, CH-4070 Basel, Switzerland; joerg.hipp@roche.com; Phone: +41-6168-22382.

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#### ETHICAL STANDARDS

All study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964. Approval was obtained from the NIH and from the Institutional Review Boards at each participating institution. Written informed consent was obtained from participants at time of enrollment in the ASNHS.

#### CONFLICT OF INTEREST

Mariana Bustamante, Lisa Sach-Peltason and Joerg Hipp are full-time employees of Roche. Daiana Cassater was full-time employee of Roche at the time of writing. Lynne Bird and Wen-Hann Tan have been paid consultants of Roche and have received funding to conduct clinical trials from Roche. Alexander Rotenberg has been a paid consultant of Roche and has received funding to conduct clinical trials from Roche; he is also co-founder of PrevEp and Neuromotion, has consulted for Cavion and Praxis, and has received research funding from Brainsway, CRE Medical, Encoded, Epihunter and Takeda.

observational study conducted at six centers in the US. Participants were prospectively followed and classified by genotype.

**Main findings:** Epilepsy was reported in a greater proportion of individuals with a deletion than a non-deletion genotype (171 out of 187 (91%) vs. 48 out of 78 (61%),  $p < .001$ ). Compared to participants with a non-deletion genotype, those with deletions were younger at the time of first seizure (age: median [95% confidence interval]: 24 [21–24] months vs. 57 [36–85] months,  $p < .001$ ), and had a higher prevalence of generalized motor seizures. Hospitalization following a seizure was reported in more children with a deletion than a non-deletion genotype (92 out of 171 (54%) vs. 17 out of 48 (36%),  $p = .04$ ). The overall prevalence of absence seizures was not significantly different between genotype groups. 46% (102/219) of the individuals reporting epilepsy were diagnosed with AS concurrently or after their first seizure.

**Conclusions:** Significant differences exist in the clinical expression of epilepsy in AS according to the underlying genotype, with earlier age of onset and more severe epilepsy in individuals with AS due to a chromosome 15 deletion.

### Keywords

seizures; epilepsy; genotype; Angelman syndrome; UBE3A; GABR; GABA; 15q11–13

## INTRODUCTION

Angelman Syndrome (AS) is a rare genetic neurodevelopmental disorder with a prevalence of about 1 in 22,000 births [1–3]. Its root cause is the lack of a functional transcript of the maternal *UBE3A* allele located on chromosome 15q11–13 in neurons (in some cases of *UBE3A* missense mutation a transcript with impaired function may be present). A complex process of regulation known as imprinting allows for the silencing of alleles based on their parental inheritance; in the case of *UBE3A*, the paternal copy of the gene is normally silenced in neuronal cells, and only the maternal allele is transcribed [4].

Several genetic mechanisms can lead to impaired maternal *UBE3A* expression and have been described previously in detail [4,5]. Two large genetic subgroups can be differentiated: deletion genotypes, which account for approximately 70% of cases and non-deletion genotypes, which comprise 30% of cases. Among individuals with a deletion, the length of the chromosomal deletion varies. Deletions of 15q11–q13 commonly occur at recurring break points, resulting in two typical deletion sizes: class 1 (Del1, ~6 Mb, ~16 genes and various non-coding regions deleted, ~40% of deletions) and class 2 (Del2, ~5 Mb, ~12 genes and various non-coding regions deleted, ~55% of deletions). Atypical deletions (DelAT, ~5%) can span chromosomal segments longer than Del1 or shorter than Del2 [6,7]. Non-deletion genotypes comprise pathogenic variants of the maternally inherited *UBE3A* allele, paternal uniparental disomy (UPD) for chromosome 15q11q13, and imprinting defects (IPD) wherein the maternal *UBE3A* allele is erroneously silenced. In addition to lack of *UBE3A* expression in the deletion subgroup, there are only single copies (haploid) of non-imprinted genes adjacent to *UBE3A*, including three GABA-A receptor subunit genes (*GABRB3*, *GABRA5*, *GABRG3*), which may contribute to a generally more impaired phenotype in those individuals with a deletion, compared with non-deletion genotypes [8,9].

The core clinical characteristics of the AS phenotype include epilepsy, intellectual disability, sleep disturbances, movement disorders such as ataxia and tremor, limited expressive language, anxiety, maladaptive behaviors and easily provoked laughter with an apparently happy demeanor [10]. Electroencephalographic (EEG) abnormalities have been identified in nearly 100% of individuals with or without epilepsy [11].

Although developmental delays in AS are often evident by six months of age, the diagnosis of AS is usually made after one year of age when the typical clinical features [12] are more apparent [10]. Notably, recent advances in genetic characterization of AS and data gathered from large cohorts in longitudinal studies have expanded our appreciation of the spectrum of clinical presentation, and it has become apparent that the lack of certain features (e.g. microcephaly, seizures) does not preclude the diagnosis of AS [13].

Epilepsy is reported in most individuals with AS, and it is considered one of the most burdensome aspects of the phenotype by both caregivers and clinicians [14,15]. Seizures usually appear within the first three years of life in the vast majority of cases, and in 50% of them, the first seizure occurred within the first 12 months of age [16]. Seizures in individuals with AS can be difficult to treat and tend to require polypharmacy; in some instances dietary and other non-pharmacological approaches are needed [17].

Here, we systematically and quantitatively investigate key seizure characteristics in the pediatric AS population and differences between AS genotypes. We focus on the features of seizures in individuals younger than 18 years of age who have been enrolled and prospectively followed in the AS Natural History Study (ASNHS) to provide a comprehensive characterization of seizures in a large population of children with AS.

## MATERIALS AND METHODS

### Participants.

The ASNHS ([ClinicalTrials.gov](https://clinicaltrials.gov) Identifier: [NCT00296764](https://clinicaltrials.gov/ct2/show/NCT00296764)) was conducted under the auspices of the Angelman, Rett, and Prader-Willi Syndromes Consortium of the NIH Rare Diseases Clinical Research Network (RDCRN). The inclusion criteria were 1) a molecular diagnosis of AS, or meeting all major diagnostic criteria for AS and three of the six minor clinical criteria as specified by the study protocol (<https://clinicaltrials.gov/ct2/show/NCT00296764>) and 2) between 1 day and 60 years of age. The exclusion criteria were: having another medical condition that was felt to obscure the AS phenotype, or prematurity <28 weeks of gestation. Enrollment began in 2006 and continued until 2014 at six sites across the United States. The study was approved by the institutional review board at each of the institutions where the data were obtained.

The ASNHS recruited 302 participants with a molecular diagnosis of AS. Data on epilepsy or absence thereof were reported and available for analysis in 299 cases. We subdivided participants into two groups according to the molecular diagnosis: individuals carrying maternal deletion (class 1, class 2 or unspecified deletions) and individuals with a non-deletion genotype (pathogenic variants of *UBE3A* (including truncating and missense pathogenic variants), UPD and IPD). Participants with any other genotypes (atypical

deletions, abnormal DNA methylation patterns and variants of unknown significance - i.e. UBE3A mutations that were “synonymous”, for coding the same amino acid) or with insufficiently characterized genotype (i.e. abnormal DNA methylation, FISH-negative) (n=22), as well as participants aged over 18 years old (n=12), were excluded from analyses. The resulting study population included 265 individuals aged between 0 and 18 years, of whom 187 were included in the deletion group and 78 in the non-deletion group (Figure 1). The distribution of ages at the baseline and for all visits is reported in Supplementary Figure 1.

### Measures.

Data regarding participant age at the time of the first seizure were available for 219 individuals; these data were gathered either at the baseline visit (if seizures pre-dated enrollment) or at a subsequent visit if seizures emerged during the follow-up period.

Information regarding seizure frequency and type was collected at all visits. Evaluations were performed at approximately 12-month intervals per study protocol; for missed visits, the information was collected at the next visit attended by the participant. The average number of visits per participant was  $3.25 \pm 2.1$  (mean  $\pm$  SD). Missed visits, study dropouts, and enrollment later during the data collection period contributed to reduction in the expected duration of follow-up.

For each individual, the following general information was used for the analyses: age at the time of AS diagnosis, age at enrollment (baseline visit) and at subsequent visits, age at time of last study assessment, and age at time of the first seizure. In each instance, age was expressed in months. The follow-up time was calculated and expressed in months.

The types of seizures experienced by the participants were reported by parents and defined by the investigators conducting the clinical assessments according to a pre-defined scheme: absence seizures were distinguished from any type of generalized motor seizures, including myoclonic, tonic, clonic, tonic-clonic and atonic seizures. An ‘other’ category was used for seizures that could not be classified into one of the above.

Medications prescribed to each patient were classified by the investigators according to their reported indication. In cases where the indication was not available, the usual indication of the drug was considered for classification purposes (Table 1). The number of anticonvulsants was calculated for every individual at each visit. Emergency (“rescue”) antiepileptic medications (e.g. per rectum diazepam) were not included as regular anticonvulsive therapy.

### Statistical analyses

Summary statistics for non-normally distributed variables were expressed as median and interquartile ranges [IQR] and compared using Mann-Whitney U test. Frequencies for categorical variables were compared using Pearson’s chi-squared test. For between-group comparisons, a p-value of .05 or less was regarded as significant and IQRs or confidence intervals [CIs] were provided where deemed appropriate.

To evaluate the incidence of seizures and hospitalizations over time in both cohorts (i.e. deletions vs. non-deletions, see Results), we used a time-to-event approach [18]. This type of analysis properly accounts for participants that either withdrew from the study before experiencing the event of interest, or that reached the end of the study without an event (“right-censoring”). In addition, since participants were enrolled and contributed data at different ages, simply deriving the fraction with seizures for the whole population would have not been deemed appropriately informative. The baseline for time-to-event analyses was each participant’s birth date, and hence the age (in months) at the time of an event or of censoring was recorded to determine follow-up time.

Non-parametric Kaplan-Meier estimators were used to describe both the incidence over time of ictal events and the hospitalization events due to seizures in deletion and non-deletion genotypes. Comparisons were made by log-rank test. Median age of event occurrence for each group was defined as the value at which the Kaplan-Meier estimator crossed the 50% threshold.

In addition, we used the semi-parametric Cox proportional hazards model to estimate the hazard ratios for each specific molecular diagnosis (i.e. Class 1 deletion, UPD, etc.) and confirmed the differences observed in the log-rank test were not biased by any specific genotype.

All statistical analyses were performed using R version 3.5.3. For time-to-event analysis, the R packages survival and survminer were used [Foundation for Statistical Computing, <http://www.r-project.org/>].

## RESULTS

### Characteristics of the study population.

We investigated features of epilepsy from participants enrolled in the ASNHS, which recruited 302 participants with a molecular diagnosis of AS. After applying age and genotype criteria (see Methods), the population analyzed included 265 individuals aged between 0 and 18 years, of whom 187 were included in the deletion genotype group and 78 in the non-deletion genotype group (Figure 1).

### Age at the first seizure

Over the course of the study, only 46 out of 265 participants in this analysis (17%) did not report the occurrence of any seizure (8% of individuals with deletions vs. 38% of participants with a non-deletion genotype,  $p < .001$ ). 219 individuals reported at least one seizure before enrollment or during the observation period (171/187 (91%) of the individuals with deletions, 48/78 (61%) of the individuals with non-deletion genotypes). The above percentages should be interpreted with caution since they depend on the age composition of the sample and the participants’ follow-up time within the study.

To account for both of the latter factors, we employed a time-to-event analysis to analyze the age of onset of seizures (see Methods, Figure 2). The median age at the time of the first seizure was 24 months [95% CI: 21–24] in individuals with a deletion genotype vs.

57 months [95% CI: 36–85] in participants with a non-deletion genotype ( $p < .001$ , log-rank test). Seventy-five percent (141/187) of individuals with deletions reported their first seizure before reaching 36 months of age, compared with only 28% (22/78) of participants with a non-deletion genotype. Furthermore, the time-to-event analysis (Figure 2), suggests that basically all individuals with deletion genotype develop epilepsy compared to only about 70% of individuals with non-deletion genotypes. In summary, individuals with deletion genotypes experience their first seizure earlier, and the overall prevalence of seizures in this group is higher than those with non-deletion genotypes.

Next, we performed a sensitivity analysis to understand if the grouping of different genotypes into deletion and non-deletion genotypes was justified (Figure 3). The time-to-event curves for the three different deletion genotypes (deletion class 1, deletion class 2, unspecified deletion) look very similar. This qualitative observation is supported by a Cox-proportional hazard model with “deletion class 1” as a reference group, which shows no differences between deletion genotypes. Furthermore, within the non-deletion genotype group, pathogenic variants of *UBE3A* (differentiating missense and truncating mutations) and UPD show a very similar time-to-event profile, while IPD has a seemingly different one, with fewer cases of seizures overall. A Cox-proportional hazard model using “deletion class 1” as a reference group shows a significant difference for all non-deletion genotypes and a trend towards a significant difference for IPD compared to the other non-deletion genotypes.

### Coincidence of age of onset of epilepsy and AS diagnosis.

Of the 219 individuals with epilepsy, 54% were diagnosed with AS before their first seizure, and 46% were diagnosed with AS at the time of their first seizure or later. In the latter group, the median time [IQR] between the first seizure and AS diagnosis was 6 months [range, 1–17]. Those with deletion ( $n=81$ ) had a shorter median time to AS diagnosis ([IQR] of 5 months [range, 1–12]) compared to those with non-deletion genotypes ( $n=21$ ) ([IQR] of 17 months [range, 5–27];  $p=.01$ ) (Table 2).

**Frequency of seizures.**—We investigated the frequency of seizures in 1-year bins based on all available data (Figure 4; Supplementary Figure 1). Individuals with deletions were more likely to report seizures of any frequency. In particular, the proportion of individuals between 24–36 months and 36–48 month of age presenting very frequent seizures (> 1/day) is higher in the group with deletions than in the non-deletion group (16.2% vs. 5.9% and 15.2% vs. 8%, respectively). Given the low sample sizes, we did not perform statistical tests. At older ages, the fraction of participants carrying a deletion and reporting very frequent seizures decreases; nonetheless, at any age in the range examined, the proportion of those with deletion reporting >1 seizure/month is higher compared to those with non-deletion genotypes. Correspondingly, the proportion of individuals with a non-deletion genotype reporting no seizures was higher at any age. Notwithstanding, a substantial number of individuals with non-deletion genotype ( $n = 21$ ) had >1 seizure/month at some point across different age groups.

**Semiology of seizures.**—Of the 219 individuals reporting seizures, 84% overall ( $n=184$ ) had at least one generalized motor seizure, which included 87% (149/171) of those with

deletion and 73% (35/48) of those in the non-deletion group (difference between groups,  $p=.03$ ). There was no difference in the percentage reporting absence seizures (overall 49%, 107/219) based on genotype (81/171, 47% deletion; 26/48, 54% non-deletion,  $p=.50$ ).

**Use of anticonvulsants.**—Information on prescribed antiepileptic drugs was available for 92% (158/171) of participants with deletions and 77% (37/48) of individuals with a non-deletion genotype. The average number of prescribed anticonvulsants increased up to 6 years of age in individuals with deletions, changing from 1.32 [0.52] drugs/individual on average [SD] at 24–36 months of age to 1.52 [0.6] drugs/individual on average at age 10–11 years, remaining stable until 15 years of age. In the participants with a non-deletion genotype, the average number of prescribed anticonvulsants decreased between 2 and 6 years of age but it increased again at 11 years of age (Figure 5).

**Hospitalization events and hospitalizations due to seizures.**—Of the entire cohort, 235 participants (89%) needed to be hospitalized for any reason at any time with no significant difference between the deletion and non-deletion groups (169/187 and 66/78 respectively;  $p=.26$ ). However, of those reporting at least one seizure, a greater proportion of the deletion group (54%, 92/171) needed hospitalization after a seizure compared to the non-deletion group (38%, 18/48;  $p=.04$ ). Based on time-to-event analysis, the probability of being hospitalized for seizures by the age of 24 months was 18% (95% CI: 12–23%) in the deletion group, versus 5% (95% CI: 0–10%) in the non-deletion group. At the age of 60 months, this probability rose to 45% (95% CI: 37–53%) for individuals with deletions versus 19% (95% CI: 10–28%) of those with a non-deletion genotype. The time-to-event curves are significantly different ( $p<.0001$ ) (Figure 6).

## DISCUSSION

We used a large dataset of individuals with AS followed longitudinally to explore the characteristics of epilepsy, one of the most frequently reported and burdensome features of this condition. In particular, we compared seizure characteristics of different AS genotypes, revealing relevant differences between non-deletion and deletion genotypes in the overall likelihood of experiencing a seizure, age at seizure onset, and frequency of seizures, as well as seizure severity based on available surrogate measures such as the need for hospitalization and anticonvulsant medications. Characterization of epilepsy in AS is relevant for both clinical practice and the development of therapeutics in this population.

### Age of seizure onset and diagnosis of AS.

Consistent with the existing literature, we found that the majority of individuals with deletion reported their first seizure before 36 months of age, most often between 24 and 36 months. In addition, we found that the first seizure in participants with non-deletion genotypes presented significantly later compared those with deletion genotypes, confirming previous observations in some smaller samples [19–21]. Different non-deletion genotypes had different time to event curves (Figure 3) with the notable exception of children having AS due to IPD showing both a later onset of seizures as well as a lower overall probability to manifest a seizure during the observation period. This may be due to the



milder overall phenotype that these individuals present, which, in some cases might reflect somatic mosaicism, though this information was not available for the cohort studied [22].

Regarding the relationship between first seizure and the AS diagnosis, 23 participants were diagnosed with AS at the time of their first seizure, possibly indicating that the ictal event precipitated diagnostic testing. 79 participants were diagnosed with AS after their first seizure, sometimes as late as 138 months following the first ictal event. This may reflect difficulties in accessing testing, but it could also indicate the need for increased awareness of AS among practitioners. Importantly, 25 participants in the seizure-before-diagnosis group had their first seizure before 12 months of age when the phenotype of AS is less recognizable. We recommend therefore a low threshold for AS testing of younger children presenting with seizures in the context of developmental delay [13]. Overall, we identified a trend towards a diagnosis of AS at younger ages in those individuals that were born more recently (Supplementary Figure 2).

### **Participants remaining free of seizures.**

As expected, given the differences in seizure incidence depending on age and genotype, we found a significant difference in the number of children reporting no seizures in the two groups. Importantly, the median age at the time of the last visit was greater than 36 months, the age by which most AS individuals present their first ictal event. However, since a substantial number of individuals may have had their last visit before the occurrence of their first ictal event, simply averaging the ages of onset of seizures could lead to biased estimates. To overcome this issue, we performed a time-to-event analysis (see Methods), which provides more reliable estimators of the proportion of individuals who had experienced seizures at any given age. Using time-to-event analysis, i.e. using non-parametric Kaplan-Meier estimators, we found that a plateau was reached for both deletion and non-deletion genotypes at about age 8 years, at which point all individuals with deletion genotypes had epilepsy and about 30% of individuals with non-deletion genotypes remained epilepsy-free.

### **Seizure frequency by age and seizure severity.**

The variation of seizure frequency in AS with age has been reported previously [13]. In our analysis, we show that in children with AS at any age, a larger proportion of individuals with deletion report seizures and a greater proportion of them report frequent seizures during the first three years of life.

The increasing number of anticonvulsants prescribed up to 6 years of age in children with deletions combined with the decrease in seizure frequency that we observed suggests general - but not complete - efficacy of the pharmacological control of seizures, in agreement with other reports [16]. In individuals with non-deletion genotypes, the number of prescribed anticonvulsants decreased between 2 and 6 years of age, consistent with the observation that a greater proportion of these children remain free of seizure at any age. Paradoxically, we observed an increase in the average number of prescribed anticonvulsants at 11 years in both groups, while an improvement of epilepsy during adolescence has been previously described

[23]. However, our sample size for this analysis was small and future studies are needed to confirm these observations.

The need for hospitalization following an ictal event may also be an indicator of severity. We found that more individuals with deletion needed to be hospitalized due to an ictal event. In children with deletions, the probability of having had a seizure by 36 months of age was 80% (95% CI: 73–84%), while the probability of having been hospitalized due to an ictal event was 31% (95% CI: 24–38%). This suggests that admissions were not purely for initial diagnostic purposes. It is likely that the events were severe enough (possibly because seizure were prolonged, occurred in clusters, or were accompanied by medical complications) to require in-hospital management or that there was significant change in the symptoms reported by the caregivers. In any case, the need for hospitalizations due to seizures either for diagnostic or therapeutic purposes persists over time, and contributes to the burden experienced by individuals with AS and their caregivers.

### **Seizure semiology.**

Semiology of seizures in AS has been reported to be similar among genotypes [24]. In this study, we compared the occurrence of generalized motor seizures and absence seizures in deletion and non-deletion groups. Absence seizures are a unique variety characterized by typical EEG features [25] and require specific treatments [26]. Though absence seizures are classically categorized as generalized (non-motor) seizures [27], this classification has recently been questioned, as some of their electroclinical characteristics fall more appropriately within the definition of focal seizures [28,29]. In our analysis, while absence seizures were equally reported in deletion and non-deletion groups, generalized motor seizures were more frequently observed in subjects with deletions. This may suggest that the molecular class of AS may predispose to distinct seizure types. However, it is important to acknowledge that absence seizures were probably underreported due to the inherent difficulties in recognizing them in everyday life.

### **Importance for future clinical trials.**

The detailed characterization of the clinical features of epilepsy in children with AS provided here is a solid basis to potentially develop genotype-specific, age-dependent endpoints and to inform the designs of future clinical research. Furthermore, this characterization may help to interpret possible adverse events in clinical trials of potential treatments for AS.

## **LIMITATIONS**

Our study has several limitations. First, these analyses were retrospective, and we had to overcome the lack of homogeneity in the data that were collected in the ASNHS participants. We chose to perform our analyses on those participants for whom reliable data for specific parameters had been collected, which may limit the generalizability of our results; parent reporting and clinicians' interpretation may also bias our findings. Moreover, the contribution of repeated measures on the same participants over time was not addressed.

Secondly, the quantification of seizure severity could be improved by considering other parameters that were not systematically collected in this study. Some features contributing to the estimation of epilepsy severity, such as seizure duration and the rate of associated complications, were not systematically collected in the study. The number of drugs utilized served as a proxy for severity, but we acknowledge the uncertainty inherent in this. Similarly, we were not able to provide information on focal seizures and seizure triggers in this study.

Lastly, the small number of participants belonging to the ends of the age spectrum we analyzed limits the ability to draw conclusions regarding them.

## CONCLUSIONS

Overall, our analysis on a large cohort of individuals with AS prospectively followed in the ASNHS shows that in individuals with deletions, seizures start earlier, are more frequent, require more anticonvulsants and hospitalizations, and are nearly universal by 8 years of age. Seizures can start prior to 12 months of age, i.e. before the diagnosis of AS is usually made. Furthermore, we also found that absence seizures are equally reported in individuals with deletion and non-deletion genotypes, whereas generalized motor seizures occur more frequently in those with deletion. We also observed the existence of a small group of non-deletion AS individuals who report frequent ictal events.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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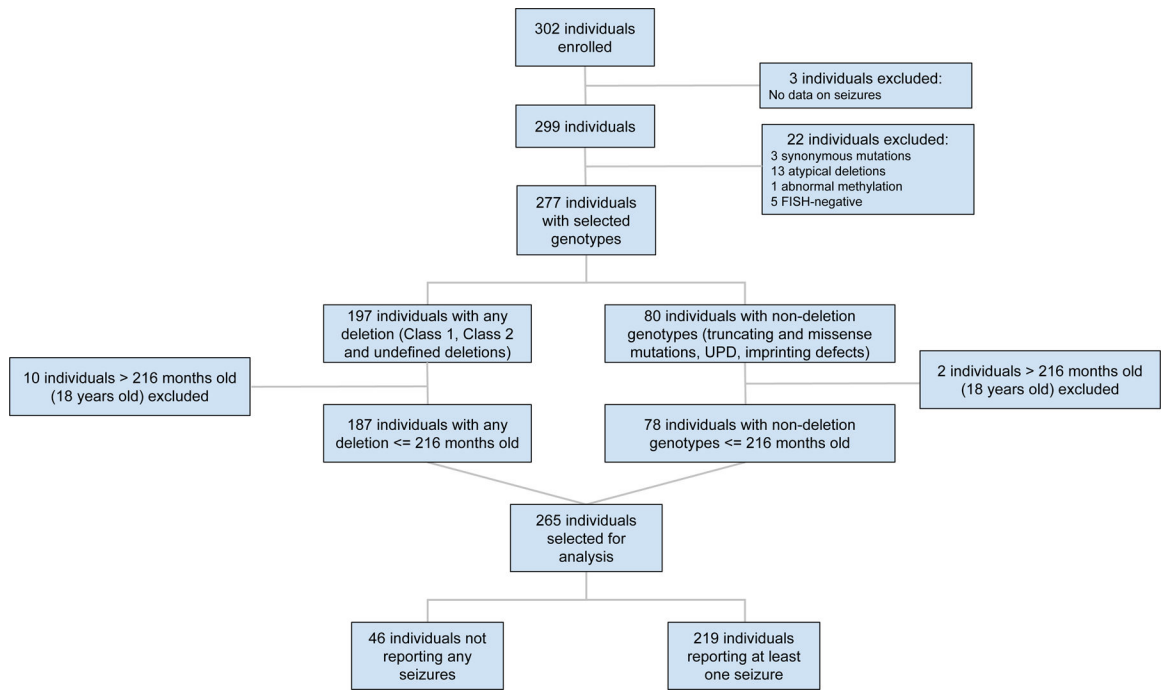
Manuscript preparation, review, and approval were solely the responsibility of the authors. The views expressed herein do not represent the official views of NCRR, ORDR, NICHD, NIH, or the Angelman Syndrome Foundation; reflect the official policies of the Department of Health and Human Services; or imply endorsement of trade names, commercial practices, or organizations by the U.S. Government.

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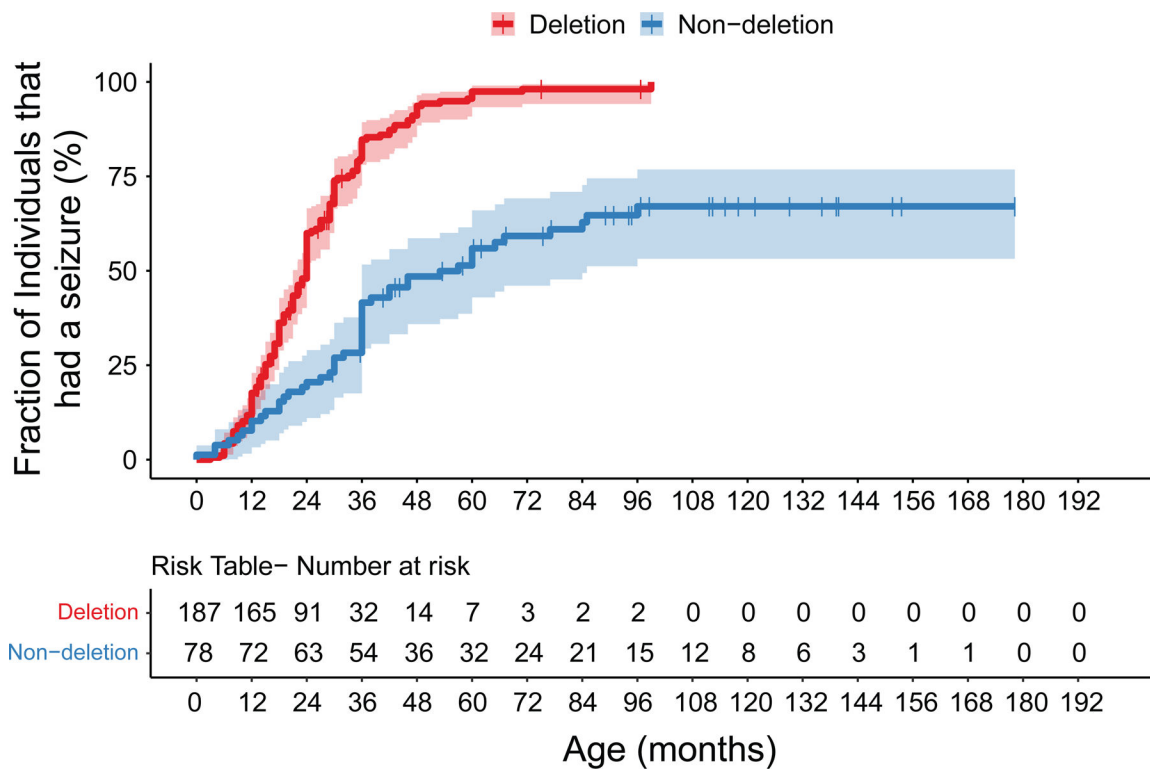
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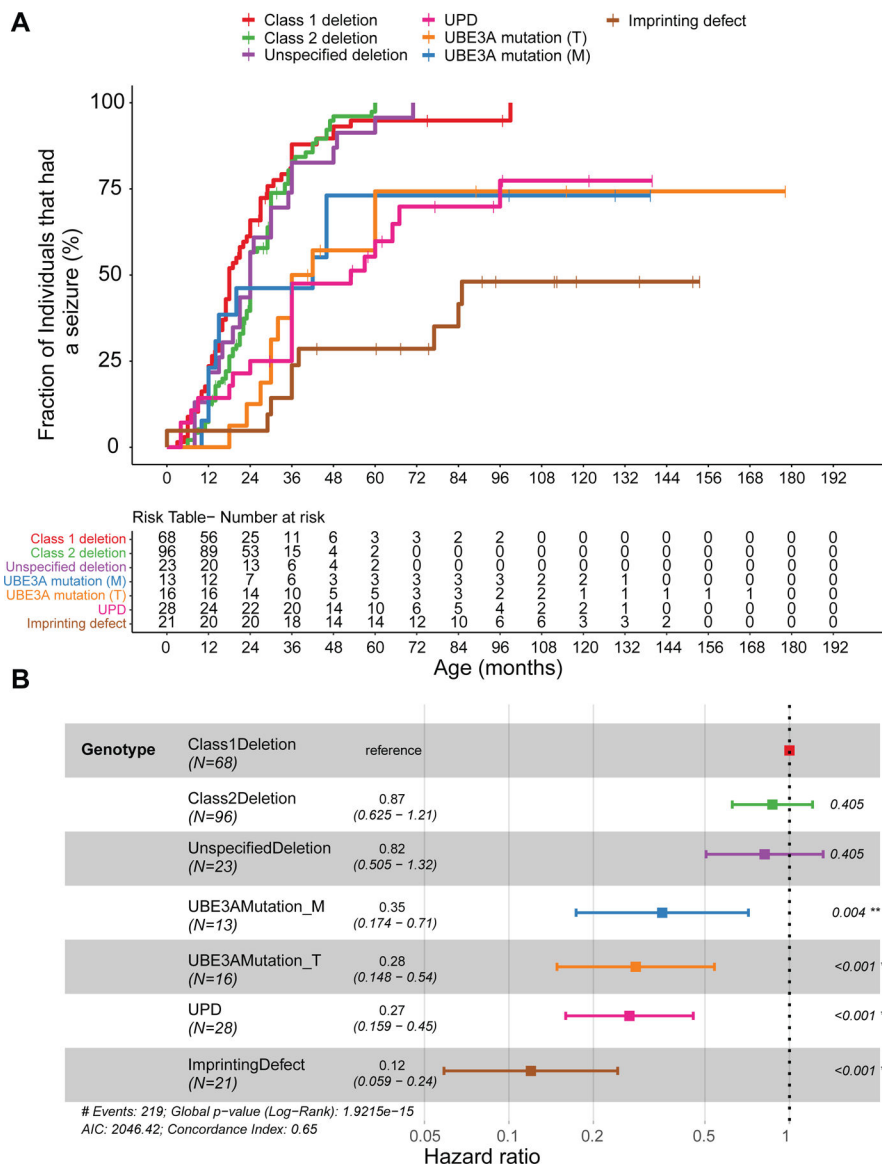
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**Figure 1.**  
Study population selection.

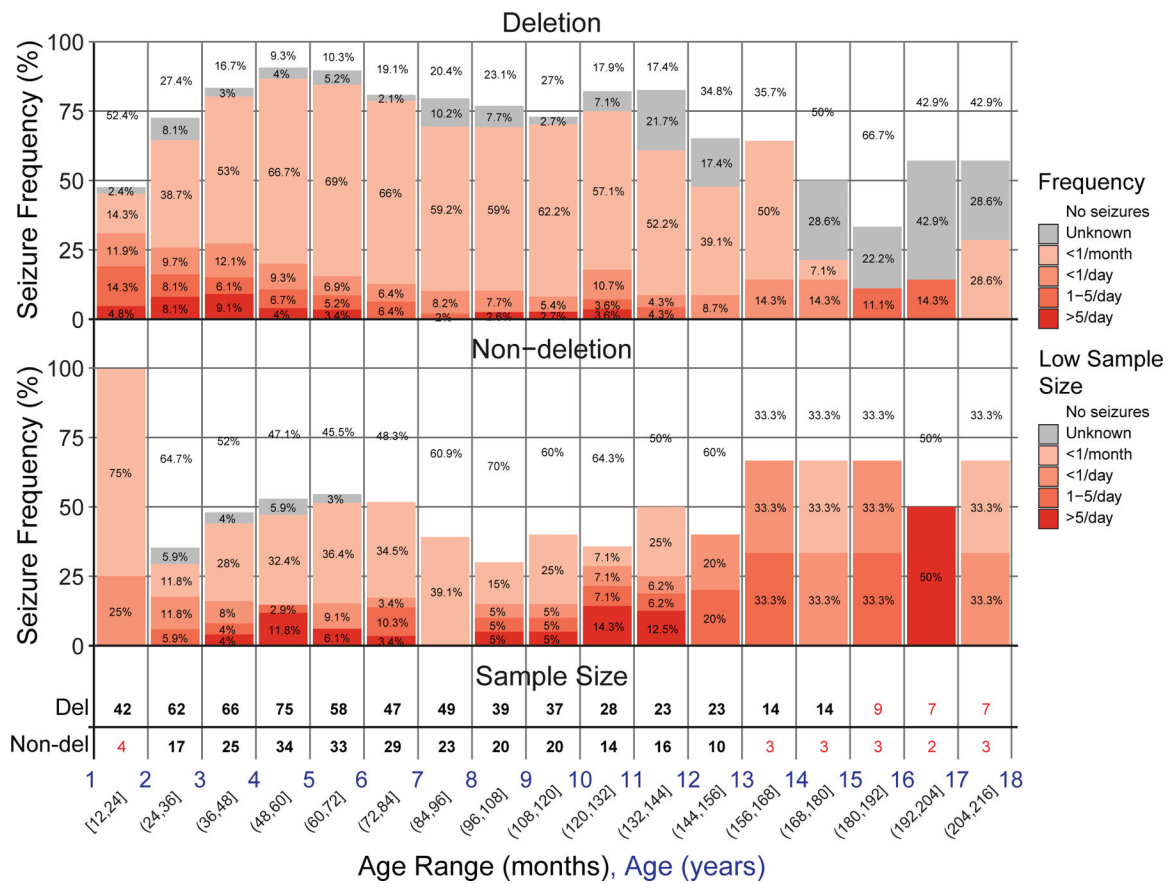


**Figure 2.** Kaplan-Meier analysis of cumulative ictal events stratified according to the individuals' grouped genotype (showing p-value of the log-rank test). Tabulated data are the number of participants at risk by genotype at 12-month intervals. Cox proportional hazard model is reported below.

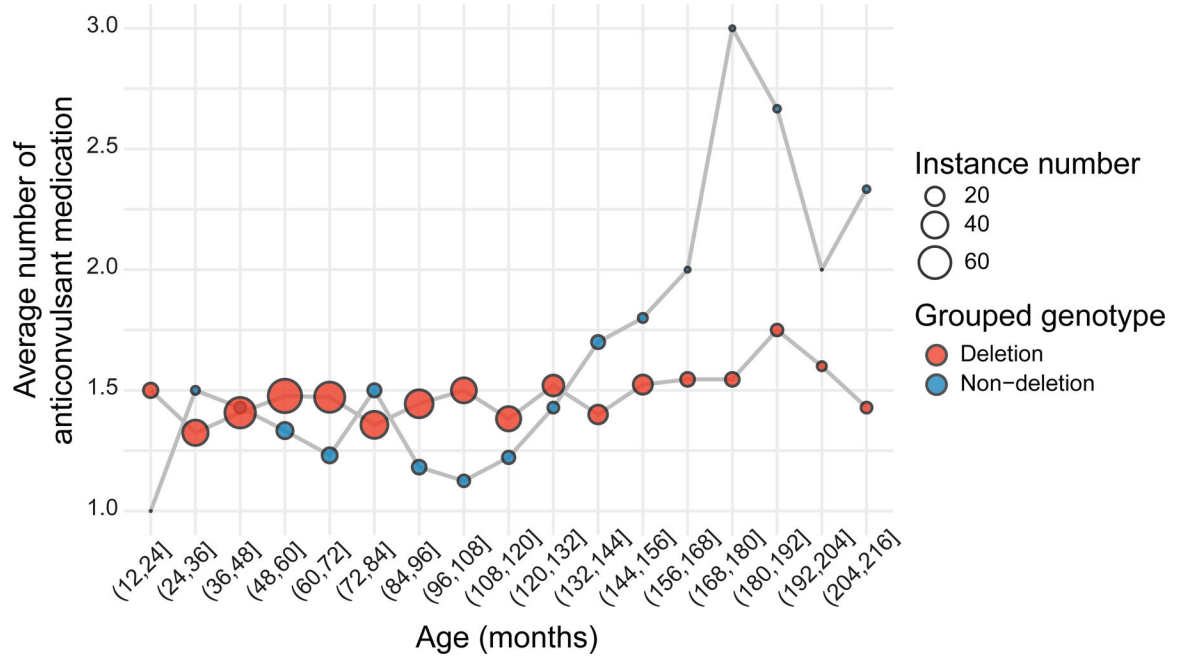


**Figure 3.** Kaplan-Meier analysis of cumulative ictal events stratified according to genotype (showing p-value of the log-rank test for comparison between the deletion and non-deletion genotypes). Of note, the probability for a patient with an imprinting defect to have presented a seizure by the age of 60 months was only 29% (95% CI 6–46%). Tabulated data are the number of participants at risk by genotype at 12-month intervals. Cox proportional hazard model is reported below. Abbreviations: UBE3A mutation (M): missense mutation; (T): truncating mutation.

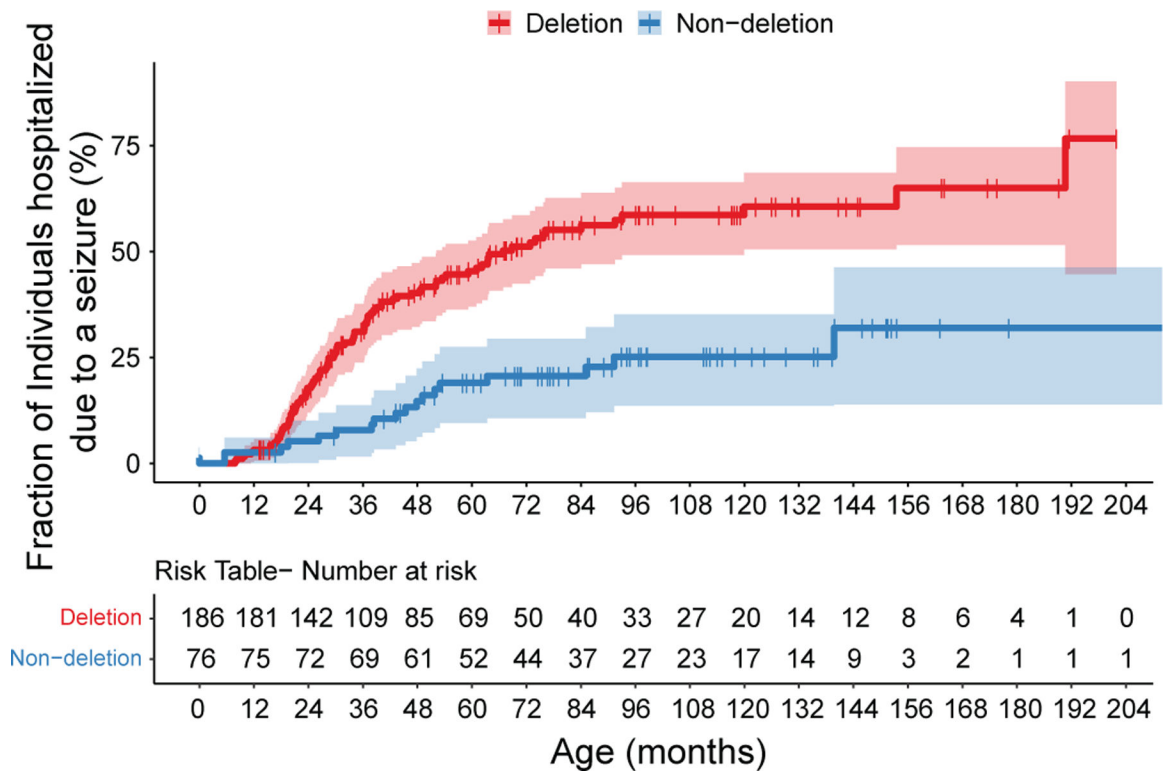




**Figure 4.** Proportion of participants reporting ictal events according to the age group and the individual genotype. The number of individuals contributing to each age bin (months, years) is indicated. Within each age group, the frequency of seizures is reported.



**Figure 5.** Average number of anticonvulsant medications by genotype and age group.



**Figure 6.** Kaplan-Meier analysis of cumulative hospitalization episodes following an ictal event stratified according to the individuals’ grouped genotype (showing p-value of the log-rank test). Tabulated data are the number of participants at risk by genotype at 12-month intervals.

**Table 1.**

List of anticonvulsants included in the analysis

Active drug
ACTH
carbamazepine
clobazam
clonazepam
clorazepate
diazepam *
ethosuximide
felbamate
gabapentin
lacosamide
levetiracetam
lamotrigine
lorazepam
methylphenobarbital
oxcarbazepine
phenobarbital
phenytoin
rufinamide
topiramate
valproate
zonisamide

\* (Except for formulations used as “rescue” medication for prolonged seizure).

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**Table 2:**

Comparisons between children with deletion and non-deletion genotypes that reported at least one seizure

	Deletion AS (n=171)	Nondeletion AS (n=48)	p-Value
No. (%) diagnosed with AS at or after their first seizure	81 (47)	21 (44)	.73 **
No. (%) with first seizure before 12 months of age	20 (12)	5 (10)	1 **
Time in months (range) between first seizure and diagnosis of AS <sup>***</sup> , median (IQR)	5 (1–12)	17(5–27)	.01 *
No. (%) individuals diagnosed with AS at time of first seizure	20 (12)	3 (6)	0.4 **
No. (%) individuals reporting generalized motor seizures, any time	149 (87)	35 (73)	<.02 **
No. (%) individuals reporting absence seizures, any time	81 (47)	26 (54)	0.4 **

\* Data compared by Mann-Whitney U test.

\*\* Data compared by Pearson's Chi-squared test.

\*\*\* in this order.