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Neurodevelopmental Profile of Siblings with Angelman Syndrome due to pathogenic *UBE3A* variants

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Abstract

Background: Angelman syndrome (AS) is a neurodevelopmental disorder caused by a lack of expression of the maternally-inherited *UBE3A* gene on chromosome 15. Individuals with AS due to a *UBE3A* mutation are more likely to have siblings who also have AS compared to those with AS due to other cytogenetic / molecular mechanisms, but it is unknown whether the developmental outcome of siblings who have AS is similar.

Method: Through an ongoing AS Natural History Study, we identified seven pairs of siblings with AS due to a *UBE3A* mutation. We compared the neurodevelopment of the first-born and second born siblings with AS participants who have a *UBE3A* mutation and have either typically-developing siblings or no siblings.

Results: Second-born AS participants due to a *UBE3A* mutation were more likely to be diagnosed at an earlier age. With the exception of higher expressive language scores among the second-born participants, no other differences were observed in the developmental and adaptive functioning skills across the different groups.

Conclusions: The presence of an older sibling with the same neurodevelopmental disorder is associated with an earlier age of diagnosis and may be associated with an improvement in

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expressive language skills; the developmental outcome of siblings with AS due to a *UBE3A* mutation is otherwise comparable.

Keywords

developmental disability; child development; phenotype; sibship; *UBE3A* mutation

BACKGROUND

Angelman syndrome (AS) is a neurodevelopmental disorder that results in severe global developmental delay with minimal or absent speech (Angelman, 1965; Clayton-Smith and Laan, 2003; Horsler and Oliver, 2006) due to the loss of the maternally-inherited *UBE3A* gene on chromosome 15q11-q13 arising from one of four molecular mechanisms, viz. a deletion on the maternally-inherited chromosome 15 that encompasses *UBE3A*, paternal uniparental disomy, imprinting defects, and mutations in the maternally-inherited *UBE3A* (Clayton-Smith and Laan, 2003; Dagli et al., 2012). Compared to AS individuals with other molecular subtypes, individuals with AS due to a *UBE3A* mutation are more likely to have siblings with AS since their mothers can be asymptomatic carriers with a 50% risk of having another child with AS. However, whether there is a difference in neurodevelopmental functioning among siblings with AS born in the same household is unknown.

We are aware of only three case reports on the neurodevelopment of siblings who have the same genetic disorder: one set each with fragile X syndrome, non-ketotic hyperglycinemia, and Angelman syndrome (Bjoraker et al., 2016; Sorensen et al., 2012; Sadhwani et al., 2018). There are no other published studies comparing the developmental profiles within sibships (i.e. biological siblings who live in the same household) with the same neurodevelopmental disorder. Through an ongoing AS Natural History Study, we have identified seven pairs of siblings who all have AS due to a *UBE3A* mutation. In this exploratory study, we seek to compare the neurodevelopment of these siblings with participants who have a *UBE3A* mutation but have either typically-developing siblings or no siblings to assess the impact of siblings on neurodevelopment in AS individuals.

METHODS

Participants

Participants in the AS Natural History study conducted from January 2006 to August 2014 at six study sites were evaluated annually. They were eligible if they had a molecular diagnosis of AS and lacked other co-morbid developmental disorders (Tan et7 al., 2011).

A total of 303 participants with AS were enrolled in the study. Thirty-one of these participants had AS due to a *UBE3A* mutation, of whom, six had no siblings, nine had only typically developing siblings (seven with older siblings and two with younger siblings), and 16 had siblings who also had AS. Typically-developing siblings were defined as those who had no learning or psychiatric issues. Of the 16 participants, we excluded one participant whose AS sibling did not participate in the study and the youngest sibling from a sibship of three AS participants. We compared the developmental profiles across four groups of AS

individuals with a *UBE3A* mutation, i.e., (a) participants with no siblings, (b) participants with typically developing siblings, (c) first-born participants in the seven sibships and (d) second-born participants in the seven sibships.

Measures

Demographic information was obtained from the primary caregivers. Information on the participant's age at diagnosis, age at which specific developmental milestones were achieved, presence of seizures, age of initiation of services, and frequency of current therapies received was collected.

Developmental functioning was assessed by a psychologist using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) (Bayley, 2005), the Mullen Scales of Early Learning (MSEL) (Mullen, 1995) or the Differential Ability Scale, Second Edition (DAS-II) (Elliot, 2007). The MSEL scale and the DAS-II were administered if the participant reached the ceiling of the Bayley-III and MSEL scale respectively. One first-born participant was administered the DAS-II and one second-born participant was administered the MSEL scales.

The Bayley-III and MSEL are often administered to individuals with developmental disabilities beyond the normative age cut-offs of the test and when used in this context generates only a developmental age of each domain rather than standard scores. In the current study, to facilitate comparison between individuals of different ages, we computed developmental quotients (DQs) for each developmental domain as determined by either the BSID-III or MSEL as was done in a previous cross-sectional study of individuals with AS (Gentile et al., 2010). The developmental quotient (DQ) for each domain is the ratio of developmental age to the chronological age multiplied by 100. If an individual was administered the DAS-II, the cognitive, receptive, and expressive DQ could not be calculated, so that sibling pair was excluded from the analyses of those domains.

Adaptive functioning was assessed using the Vineland Adaptive Behavior Scales, Second Edition (VABS-II; Sparrow et al., 2005). Standard scores (mean 100, standard deviation 15) were generated for each developmental domain.

Approximately 37% of the participants returned for more than one visit, with an interval of at least a year between visits. If a participant was evaluated multiple times, we used the neurodevelopmental scores from the visit at which participant was: (i) at least four years of age (since IQ begins to stabilize at that age (Weinert and Hany, 2003)); and (ii) at a developmental age closest to his/her sibling.

Data Analyses

Descriptive statistics were calculated, including mean and standard deviation for continuous variables, and frequency counts for categorical variables. The Kruskal-Wallis test was used to compare the four groups for continuous variables while the Wilcoxon rank-sum paired test was used to compare first-born and second-born participants on continuous variables. Fisher's exact test was used to compare the four groups on categorical variables.

RESULTS

Second-born participants were diagnosed at a significantly younger age than first-born participants (Table 1). We also examined access to, and frequency of, therapies that the participants received (Table 1). Second-born participants began Early Intervention (EI) services at a younger age; however, this difference did not reach statistical significance possibly due to the small sample size. No statistically significant differences were found between the four groups regarding the frequency of current therapies received.

In terms of performance on tests of developmental and adaptive functioning, second-born participants had statistically higher DQs than the first-born participants in the expressive language domain ($p=0.03$). The receptive communication domain DQ on the Bayley-III and the socialization domain standard score on the Vineland-II were at least 0.5 SD higher in the second-born participants compared to first-born participants, although this difference did not reach statistical significance. There were no other differences between the four groups (Table 1).

DISCUSSION

The overall goal of this exploratory study was to compare the neurodevelopment of siblings with AS due to a *UBE3A* mutation who are living in the same household with AS participants who have a *UBE3A* mutation and have either typically-developing siblings or no siblings. To the best of our knowledge, other than the three case reports stated above, there have not been any published studies comparing the neurodevelopment within sibships with the same neurodevelopmental disability.

We found that, not surprisingly, second-born participants were diagnosed at a younger age probably because the index of suspicion for AS is much higher once a previous child in the family has been diagnosed with AS.

In terms of developmental and adaptive functioning, our analyses indicated higher scores in expressive communication in the second-born siblings. However it is important to note that the analysis for expressive language DQ was based on six pair of siblings rather than seven pairs as one participant was administered the DAS-II, which does not generate a comparable expressive DQ. In addition among the six pairs of siblings, only two pairs had use of single words, and in both pairs the second-born had higher expressive DQs than the first born participants which may contribued to the overall difference in the expressive language skills among the siblings; in the remaining four sibling pairs, both first-born and second-born participants had limited consonant-vowel sounds. Alternatively, it is also possible that the higher expressive language skills in the second-born participants may be because a majoirty of our second-born participants were female who are known to have better language development than males at younger ages (Gleason & Ely, 2002). Whether this gender difference holds true for Angelman syndrome needs to be investigated in future studies. No other statistically significant differences were found in other developmental domains, but it is possible that our small sample size precluded our ability to detect small differences between these groups. However, it is equally, or perhaps more likely that the underlying

genetic defect (i.e., loss of *UBE3A* expression) in participants with AS has a far greater influence on their developmental trajectory than other factors.

In conclusion, this is the first study to compare the developmental profiles of siblings who have the same neurodevelopmental disability due to a genetic syndrome. We found that the presence of an older sibling with the same neurodevelopmental disorder is associated with an earlier age of diagnosis, but otherwise there is no difference in developmental functioning among siblings, at least in childhood. However, the developmental profile of these participants may change over time. Hence, it is important to continue large-scale longitudinal studies with ongoing developmental assessments to assess whether similar trends in development persist at later ages. In addition, future studies should investigate the levels of parental stress and psychosocial functioning in families with multiple children with the same neurodevelopmental disorder.

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Table 1.

Achievement of developmental milestones, therapy frequency and developmental and adaptive functioning of participants with Angelman Syndrome

	Participants without Siblings (n=6)	Participants with typically developing siblings (n=9)	Participants with AS siblings (n=14)		p^a	p^b
			First born (n=7)	Second born (n=7)		
Sex (Male)	3	5	6	2	0.22	0.10
Mean Age at Assessment in this study (SD) [months]	98.0 (48.7)	67.1 (34.9)	84.2 (35.1)	62.1 (31.4)	0.35	0.13
Mean Age of Diagnosis in months (SD)	47. 2(30.4)	29.1 (12.4)	46.4 (26.2)	20.9 (15.9)	0.16	0.02
Mean Age at Walking in months (SD)	35.3 (15.6)	31.1 (13.6)	29.8 (9.2)	26.5 (7.4)	0.82	0.42
Early Intervention start age [months]	13.2 (6.6)	13.5 (6.2)	15.6 (2.9)	5.75 (4.0)	0.05	0.09
Therapy						
Physical therapy *	1.9 (1.1)	1.6 (0.8)	1.5 (0.9)	1.0 (1.2)	0.43	0.41
Occupational therapy *	1.9 (1.1)	1.6 (0.97)	2.0 (1.2)	1.8 (1.5)	0.85	0.77
Speech therapy *	2.3 (1.5)	2.4 (1.0)	2.0 (1.2)	2.2 (1.8)	0.83	1.0
Other therapy ^	1.0 (1.8)	0.5 (1.06)	2.2 (2.6)	2.3 (2.5)	0.15	1.0
Total therapy	7.0 (4.9)	6.0 (2.7)	7.7 (4.0)	7.2 (4.9)	0.84	1.0
Bayley-III/Mullen Mean DQ (SD)						
Cognitive	30 (13.9)	43 (14.8)	36 § (15.0)	46 § (17.0)	0.33	0.31
Receptive	26 (14.2)	33 (16.0)	30 § (7.9)	41 § (12.5)	0.23	0.06
Expressive	17 (10.7)	24 (10.5)	18 § (9.6)	24 § (13.4)	0.42	0.03
Fine motor	33 (20.9)	40 (16.8)	34 (11.0)	49 (22.3)	0.48	0.16
Gross motor	24 (12.7)	32 (10.3)	32 (18.7)	44 (20.5)	0.18	0.11
VABS-II Mean Standard Scores (SD)						
Adaptive Behavior Composite	55 (8.9)	59 (8.7)	60 (5.5)	63 (9.1)	0.47	0.53
Communication	53 (11.2)	61 (11.0)	58 (8.2)	60 (7.8)	0.54	0.67
Daily Living Skills	57 (11.8)	59 (10.6)	62 (6.4)	63 (12.8)	0.71	0.81
Motor Skills	56 (7.2) **	60 (5.6)	63 (6.2)	68 (11.2)	0.17	0.20
Socialization	60 (9.8)	66 (9.0)	63 (7.9)	71 (10.5)	0.26	0.06

One sibling pair had missing therapy data. VABS-II= Vineland Adaptive Behavior Scales

* Therapy averages are measured times/week (0.25 = 1x/month, .5= 1x/month)

^ Other therapy includes, but is not limited to: hippotherapy, swimming, music, orientation and mobility, and autism interventions

§ DQs for these domains were calculated based on six of the seven sets of sibling because one of the participants in the 7th sibling set was administered the Differential Abilities Scales, second edition (DAS-II), which could not be used to calculate developmental age and hence DQ

** Missing score for one participant

a p values examining differences between the four groups

b p values examining differences between first-born and second-born participants