Title: Developmental Milestones in Children with Angelman Syndrome: Findings from the Angelman Syndrome Natural History Study

Authors: Anjali Sadhwani, Lynne M. Bird, Carlos A. Bacino, Steven A. Skinner, Sarika U. Peters, Logan K. Wink, Craig A. Erickson, Nicole LaValle & Wen-Hann Tan

Introduction: Angelman syndrome (AS) is a rare neurodevelopmental disorder with a prevalence of 1 in 15,000 (Buckley, Dinno, & Weber, 1998; Clayton-Smith & Laan, 2003; Kyllerman, 1995). Individuals with AS have global developmental delay, severe intellectual disability, and minimal or absent speech (Clayton-Smith & Laan, 2003). AS results from the loss of expression of the maternally-inherited copy of \textit{UBE3A} in the brain due to one of four mechanisms, viz. a deletion on maternal chromosome 15q11q13, paternal uniparental disomy (UPD) of chromosome 15, an imprinting defect, or a mutation in the maternally-inherited copy of \textit{UBE3A} (Dagli, Buiting, & Williams, 2011; Fang et al., 1999). Although AS is a neurodevelopmental disorder that was described over 50 years ago, the ages at which these individuals achieve various developmental milestones have not been systematically studied. The AS Natural History Study initiated in 2006 is a longitudinal study in which each participant is evaluated at a study site at regular, typically annual, intervals. The purpose of this presentation is to provide information about achievement of developmental milestones among individuals with AS.

Method: At each study visit, parents were interviewed about the ages at which the participants achieved specific motor and language skills.

Results: We have enrolled 302 individuals with a cytogenetic or molecular confirmation of AS (age range: 5 months to 40½ years old) in the Natural History study. Information on the achievement of developmental milestones was available on 296 participants, 72% of whom had a deletion, 11% had a UBE3A mutation, and the remaining 17% had UPD, imprinting defect, or abnormal methylation not further classified. Our data revealed that the median age [interquartile range] of sitting unsupported was 10 [8,13] months, crawling on all 4 limbs was 20 [15,28] months, pulling to stand was 21 [15,27] months, and walking independently was 36 [26, 47] months. The median age [interquartile range] of transferring objects between hands was 15 [9,24] months and having a pincer grasp was 24 [18, 38] months. The median age [interquartile range] of pointing or gesturing to indicate their needs was 30 [18, 48] months, of using sign language was 35½ [24, 54] months, and (among the 110 participants with verbal language), of speaking first words was 36 [24,47] months. We also found that most participants who had a deletion in the chromosome 15 AS critical region achieved these milestones at a later age than those who had either UPD / imprinting defects. We will present analyses of other developmental milestones and provide further breakdown of the age of achievement of these milestones by different molecular subclasses.

Discussion: Our findings indicate individuals with AS achieve milestones at a much slower rate than the typical developing children. However there are differences in age of achievement of milestones across different AS subtypes. The results of our study should help clinicians provide parents with a more accurate prognosis on the developmental trajectory in AS children, and facilitate the ability of clinicians to determine whether an AS child is achieving milestones at the expected rate, failure of which may be a sign of subclinical seizures or other medical complications.

References/Citations: