Title: Longitudinal Analysis of EEG Power and Cognition in 15q11.2-Q13.1 Duplications (Dup15q Syndrome)

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Introduction: Duplications of 15q11.2-q13.1 (referred to as dup15q syndrome) are one of the most common copy number variants associated with autism spectrum disorder (ASD) and intellectual disability (ID) (Finucane et al., 2016). This chromosomal region contains genes critical to brain development, including three GABAα receptor genes and ubiquitin ligase E3A (Ube3a). Dup15q syndrome is also associated with epilepsy and delays in motor skills and adaptive behavior (Distefano et al., 2016). Recently, an electrophysiological biomarker of this syndrome has been identified in the form of elevated beta band power (12-30 Hz) which likely relates to the underlying overexpression of GABAα receptor genes. This biomarker holds tremendous potential as a meaningful marker of target engagement with pharmacological therapies. However, the stability of this biomarker over time has not yet been established, particularly relevant given its association with age and epilepsy. We asked whether beta power was stable over time in young children with dup15q syndrome and whether the development of epilepsy related to change in beta power.

Methods: As a subset of a larger cohort study of children with Dup15q syndrome, we examined a group of children with dup15q syndrome at repeated time points, coinciding with their clinical evaluations at UCLA. Time span between assessments ranged from 11-22 months. Genetic reports confirmed isodicentric or interstitial duplications of chromosome 15q in all participants, three male (42, 44, and 57 months old), and three females (15, 28, and 55 months old). One participant developed seizures between the first and second time points. No other participants had epilepsy. Verbal and Nonverbal developmental quotients (VDQ; NVDQ) were calculated at each visit based on standardized assessments (Mullen Scales of Early Learning). EEG data were processed using EEGlab. A bandpass filter was used to filter the EEG data from 1-50 Hz, and both visual inspection and independent component analysis (ICA) were used to remove physiological artifacts. Relative beta1 (12-20Hz) and beta2 (20-30Hz) power were computed and averaged across the whole scalp. Paired sample t-tests were used to assess change in beta power between visits.

Results: Average VDQ and NVDQ at visit one were 54.21 (SD=31.54), and 62.68 (SD = 27.19), respectively. Average VDQ and NVDQ at visit two were 48.90 (SD = 33.32), and 43.33 (SD = 23.88). VDQ did not significantly differ between visits (t(5) = 1.409, p = .218), however NVDQ was significantly lower at the second visit (t(5) = 3.119, p = .026) suggesting a greater divergence from typical development over time. Whole-scalp resting-state relative beta1 and beta2 power did not differ between visits (t(5) = - .907, p = .406), (t(5) = .596, p = .577). However, visual inspection of the EEG data revealed that, in the participant who developed epilepsy, beta1 and beta2 power was markedly reduced at the second visit compared with the first.

Discussion: EEG power in the beta band in children with dup15q syndrome appears to be stable across multiple measurements, thus supporting its consideration as a biomarker of the syndrome. Further longitudinal research is needed to explore the temporal relation between epilepsy, beta power, and cognitive function in this population, especially as the widespread use of microarray testing of all infants with developmental delay has led to genetic diagnoses being commonly made prior to the onset of epilepsy and neurodevelopmental disorders (Schaefer & Mendelsohn, 2013).

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