2021 Gatlinburg Conference Poster Submission

Title: Early Developmental Concerns in 22q11.2 Deletion and Duplication Carriers

Authors: Eve Kortanek[1], Shafali Jeste[2], Carrie Bearden[2], Erin Nosco[2], Gabrielle MacNaughton[2], Amy Lin[2]

Introduction: 22q11.2 deletions and duplications are among the most common copy number variations (CNVs) associated with neurodevelopmental disorders. Deletions cause multiple medical comorbidities which can lead to velo-cardio-facial syndrome and are also highly penetrant for schizophrenia later in life. Although these CNVs are often diagnosed early in development, few studies have examined their early developmental features. Developmental delays in this population often go undetected, remain untreated, and may worsen over time, resulting in profound effects on daily functioning. Studying early development in children with 22q11.2 deletions (DEL) and duplications (DUP) could facilitate early intervention, improve developmental outcomes, and enable us to prospectively examine early features of neurodevelopmental disorders (e.g., Autism Spectrum Disorder). This study aimed to investigate general development and social communication skills in 22q11.2 CNV carriers age 5 and under.

Method: A REDCap[A, B] survey including two standardized caregiver questionnaires—the Ages & Stages Questionnaires, Third Edition (ASQ-3[C]; a global developmental screener) and the CSBS DP Infant/Toddler Checklist (ITC[D]; a screener for social communication delays)—was used to assess early developmental profiles in children with 22q11.2 CNVs. The survey was distributed via social media, and eligibility criteria included having a child age 5 or under with a genetic diagnosis of 22q11.2 DEL or DUP. The final sample consisted of 93 caregivers (DEL: N = 63, M = 2.6 yrs, SD = 1.4; DUP: N = 30, M = 2.9 yrs, SD = 1.4). In addition to the ASQ-3, caregivers of 22q11.2 CNV carriers age 6–24 months completed the ITC (DEL: N = 23, M = 1.5 yrs, SD = 0.4; DUP: N = 10, M = 1.5 yrs, SD = 0.5). Children scoring below or close to the referral cutoff (2 SD below the mean)[E] in any given ASQ-3 domain (Problem Solving, Personal-Social, Fine Motor, Gross Motor, or Communication) were classified as demonstrating developmental concerns, with those scoring below or close to the cutoff in 3–5 domains flagged for global developmental concerns. Scores at least 1.25 SD below the mean on the total ITC indicated social communication concerns.[D] Chi-square tests for independence (α = .05) were performed to examine relationships between CNV status and caregiver responses.

Results: Greater than 85% of caregivers of children with 22q11.2 DEL and 22q11.2 DUP reported developmental concerns in at least one ASQ-3 domain. Additionally, a high proportion (> 60%) of caregivers reported social communication concerns as well as global developmental concerns. Of 22q11.2 CNV carriers below the cutoff in any ASQ-3 domain, 55% of 22q11.2 DEL carriers and 83% of 22q11.2 DUP carriers were below the cutoff in 2–4 other domains. Moreover, in each domain of the ASQ-3, more than half of caregivers in each group reported developmental concerns. Overall, proportions of reported concern were similar between 22q11.2 DEL and DUP carriers, with the exception of global concerns [X^2 (1, N = 93) = 5.3, p = .021] and gross motor concerns [X^2 (1, N = 93) = 9.2, p = .0024] reported significantly more in 22q11.2 DUP. Proportions of reported neuro-developmental diagnoses [X^2 (1, N = 93) = 4.5, p = .033], as well as reports of genetic testing prompted by developmental concerns [X^2 (1, N = 93) = 10.9, p < .001] and family history concerns [X^2 (1, N = 93) = 11.7, p < .001], were also higher among 22q11.2 DUP carriers. However, of 22q11.2 CNV carriers age 2 and above who were below the cutoff in every ASQ-3 domain, only 50% had a reported neurodevelopmental diagnosis. Furthermore, of those reported to receive behavioral intervention, only 17% of 22q11.2 DEL carriers and 38% of 22q11.2 DUP carriers had a reported neurodevelopmental diagnosis.

Discussion: Overall, the majority of 22q11.2 CNV carriers had reported developmental concerns. Notably, proportions of reported neurodevelopmental diagnoses were lower than expected in both 22q11.2 DEL and DUP carriers, even among children receiving diagnosis-contingent intervention services, suggesting an underreporting of neurodevelopmental diagnoses in our sample. Nevertheless, neurodevelopmental diagnoses and developmental concerns were reported more prevalently in 22q11.2 DUP. While recent findings demonstrate an increased prevalence of neuropsychiatric disorders in 22q11.2 DUP, our results deviate from the observation that 22q11.2 DEL confers higher risk for developmental delay.[F] As such, the developmental profiles of 22q11.2 DUP carriers in the present study might be uniquely representative of those detected early due to more severe symptomatology. In all, high proportions of reported developmental concerns in both 22q11.2 DEL and DUP suggest the need for close monitoring of development in 22q11.2 CNV carriers in order to initiate early interventions.

References:

A. Harris P.A., Taylor R., Thielke R., et al. (2009). Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform, 42(2*), 377-381.
B. Harris P.A., Taylor R., Minor B.L., et al.; REDCap Consortium. (2019). The REDCap consortium: Building an international community of software partners. *J Biomed Inform*, *95*, 103208.
C. Squires J., & Bricker D. (2009). Ages & Stages Questionnaires®. Third Edition. (ASQ-3™): A Parent-Completed Child Monitoring System. Baltimore, MD: Paul H. Brookes.
D. Wetherby, A.M., & Prizant B.M. (2001). Communication and Symbolic Behavior Scales Developmental Profile Infant/Toddler Checklist. Baltimore, MD: Paul H. Brookes.
E. Squires J., Twombly E., Bricker D., et al. (2009). ASQ-3™ User's Guide. Baltimore, MD: Paul H. Brookes.
F. Olsen L., Sparsø T., Weinsheimer S.M., et al. (2018). Prevalence of rearrangements in the 22q11.2 region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: a case-cohort study. *Lancet Psychiatry, 5(7),* 573-580.

[1] Carleton College
[2] University of California, Los Angeles Semel Institute for Neuroscience and Human Behavior