Title: Familial Autism Risk and the Emerging Autism Phenotype: A Comparison of Toddlers from Simplex and Multiplex Families

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Introduction: Risk for autism spectrum disorder (ASD) is largely attributable to genetic factors, which in turn can influence clinical presentation (Robinson et al., 2014). Children of multiplex (MPX) families, families with two or more children with ASD, are at high familial risk for ASD while those from simplex (SPX) families, families with only one affected child, are at low familial risk for ASD. Critically, stronger familial influences on overall genetic risk for ASD, as in MPX cases, is associated with less severe ASD presentation (Robinson et al., 2014). Indeed, phenotypic differences among individuals with ASD from SPX and MPX families have been reported (e.g., Berends et al., 2019; Taylor et al., 2015), however, findings are inconsistent, and few studies have included infants and toddlers. The aim of the current study is to examine differences in cognitive functioning, language ability and autism symptom severity among infants and toddlers with (emerging) ASD from MPX and SPX families.

Method: This study used data collected at as part of two larger behavioral intervention RCTs for infants and toddlers showing behavioral features of ASD (P50HD055784-5843 & P50HD055784-8487, PI: Connie Kasari). Data from the baseline timepoint were included in the current study. Familial risk groups were defined as follows: at least one sibling with ASD (MPX), no family history of ASD in first, second, or third degree relatives and ≥ 1 typically-developing older sibling (SPX-Sib), and first-born children with no family history of ASD in first, second, of third degree relatives (SPX-FB). The final sample for the current study consisted of 121 infants and toddlers (MPX=29, SPX-Sib=38, and SPX-FB=54) who qualified for enrollment in the original RCTs by virtue of having elevated scores on the Autism Diagnostic Observation Schedule (ADOS-2; Lord, Rutter, et al., 2012). Mean age at enrollment was 20.9 months (SD=5.5). Participants were predominantly non-white (57.9%) and male (77.8%). Approximately 22.3% of participants had an ASD diagnosis from a community provider prior to enrollment. Scores from the ADOS-2 and Mullen Scales of Early Learning (MSEL; Mullen, 1995) administered at baseline were used to address study aims.

Results: To test the effect of familial risk status on cognitive ability, an ANCOVA was conducted using developmental quotient (DQ) scores calculated from the MSEL. The model revealed significant group differences in DQ after controlling for age, sex, and study cohort ($F_{(2,111)}$=5.70, p=.004). Planned contrasts (MPX vs. SPX-FB and MPX vs. SPX-Sib) reveal that MPX children had significantly higher DQ scores than both SPX-FB children (p=.022) and SPX-Sib children (p=.002). Approximately 69% of participants presented with expressive language (EL) delay and 79% with receptive language (RL) delay (defined as MSEL EL or RL T-score ≤ 35). To test whether the proportion of participants with EL and RL delay differed by group, two binary logistic regressions were conducted predicting presence of language delay from familial risk status, age, sex, and nonverbal DQ. The omnibus model predicting EL delay was significant (p<.001) and accounted for 41% of the variance in EL delay. The overall effect of familial risk status was significant (Wald $\chi^2(2)$=6.31, p=.043) and the model revealed that SPX-Sib children were 6.57 times as likely as MPX children to present with EL delay (p=.014). The omnibus model predicting RL delay was significant (p<.001) and accounted for 55% of the variance in RL delay, though the effect of familial risk status was not significant (p=.177). To test for group differences in autism symptom severity, an ANCOVA was conducted using ADOS-2 comparison scores. There was a significant effect of familial risk status after controlling for age, sex, study cohort, and ADOS-2 module ($F_{(2,113)}$=5.322, p=.006). Planned contrasts revealed that the MPX group had significantly lower scores, indicative of less severe autism symptoms, than the SPX-FB group (p=.012) and SPX-Sib group (p=.006).

Discussion: In line with past work, results reveal differences in cognitive functioning, language skills, and autism symptom severity among children with ASD from multiplex and simplex families. Both SPX-Sib and SPX-FB children had more severe cognitive delay and more severe autism symptoms compared to MPX children. While the majority of children presented with language delay, SPX-Sib children had significantly greater odds of expressive language delay relative to MPX children. These findings suggest that the simplex-multiplex differences observed among older children and adults with ASD may originate very early in symptom development, as has been suggested in some longitudinal work (Lord, Luyster, Guthrie, & Pickles, 2012). Future work is needed to (1) longitudinally compare developmental trajectories across multiplex and simplex groups and (2) to evaluate etiological factors (e.g., genetic risk) and developmental factors (e.g., parent-child dynamics) that may contribute to differing phenotypes.

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