Title: Maternal Health Complications, ASD Diagnostic Prevalence, and Symptoms Among Individuals with Likely Gene Disrupting Mutations

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Introduction: While the mechanisms that cause and contribute to autism spectrum disorder (ASD) are not yet fully explained, current research evidences both genetic and environmental contributors to ASD (Chaste & Leboyer, 2012). A number of likely gene disrupting (LGD) mutations, or mutations that cause single allele damage resulting in hindered protein function, are strongly linked to ASD (O’Roak et al., 2012, Iossifov et al., 2014). However, notable phenotypic heterogeneity exists within LGD mutations (Hudac et al., 2017)—while certain mutations are strongly associated with ASD, not all individuals with an LGD mutation in an ASD-associated gene will meet full diagnostic criteria for ASD (Guo et al., 2018). Environmental factors have also been associated with ASD, including pregnancy complications and prenatal exposure to fever (Lyall et al. 2012, Brucato et al., 2017, Spann et al., 2019). It is not currently known whether these prenatal factors influence ASD symptoms and presentation among individuals with ASD-associated mutations. As such, this study investigated associations between ASD diagnosis, ASD symptoms, and prenatal health complications in a sample of individuals with ASD-associated LGD mutations.

Method: This analysis included 157 (53.5% male) participants between the ages of 2-28 years with a pathogenic or likely pathogenic ASD-associated LGD mutation; LGDs were confirmed via whole exome sequencing or prior testing from clinical genetic reports. Caregivers were administered a phenotypic assessment battery, including a structured pregnancy and medical history interview, the Vineland-II or Vineland-III (Sparrow, Balla, and Cicchetti, 2005; Sparrow, Cicchetti, & Saulnier, 2016), and the Social Responsiveness Scale—2 (Constantino & Gruber, 2012). The majority of participants (n = 120) were administered cognitive assessments and diagnostic assessment for ASD, including the ADOS and ADI (Lord, Rutter, & Goode, 1989; Lord, Rutter, & Le Couteur, 1994). DSM-5 diagnoses of ASD were confirmed (65.6%) or disconfirmed by a licensed psychologist. Chi-square and t-tests were conducted to examine relationships between maternal complications and ASD diagnosis and symptom severity.

Results: Contradictory to predictions, maternal infection during pregnancy was associated with decreased likelihood of ASD diagnosis, ($X^2$ (1) = 7.77, $p < .01$). Gestational diabetes was associated with increased likelihood of ASD diagnosis, ($X^2$ (1) = 4.23, $p < .05$), while hypertension and pre-eclampsia were not associated with ASD. Maternal health complications were not associated with adaptive behavior, IQ, or ASD symptom severity.

Discussion: Among individuals with LGD mutations, individuals whose mother experienced an infection during pregnancy were less likely to meet diagnostic criteria for ASD, while individuals whose mother experienced gestational diabetes were more likely to meet ASD criteria. Given that these groups did not differ in ASD severity as measured by the SRS-2, the factors driving these diagnostic discrepancies are currently unclear. Nevertheless, these results indicate that prenatal environment may indeed play some role in ASD risk, and further investigation is warranted among individuals with ASD-associated LGD mutations.

References:


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