Commentary

Interpretion of the Environmental Impact on Autism Spectrum Disorder

Fengyu Zhang, Claude Hughes

Autism is a neurodevelopmental disorder with complex etiology, comprising both genetic and environmental factors and their interactions(1). Family and twin studies have indicated that ASD is highly heritable, with that recurrent sibling risk of autism was approximately 20%, and the concordance rate was 96-99% in monozygotic (MZ) twins and 44-60% in dizygotic (DZ) twins(2, 3). A population-based family study with a whole-genome genotyped SNP data shows that 52% of the risk for autism is attributed to the common genetic variants(4). Despite the evidence that autism is heritable, only a limited number of common genetic variants have been associated with ASD (5-7). A recent genome-wide association meta-analysis of 18,381 individuals with ASD and 27,969 controls identified five loci associated with ASD at a genome-wide significance and seven SNPs shared with schizophrenia (SCZ), major depression (MDD) and educational attainment (8). Autism is highly heterogeneous, and it is the clinical heterogeneity that affects the capability to identify common genetic variants that explain the heritability of autism (9).

As advances in the next-generation sequencing technology have progressed over the past decade, many efforts have been made to detect rare functional variants in individuals with ASD. While rare copy number variants (CNVs) contributes to the risk of autism(10), whole exome-sequencing studies suggest that hundreds of rare *de novo* mutations play some roles, in which substantial evidence implicates a few specific genes (*CHD8, KATANAL2, SCN2A, NTNG1*)(11). These rare variants, highly penetrant or altering proteins, provide a good insight into the biology of autism (12), they may account for little heritability. Since some *de novo* mutation may be caused by exposure to environmental mutagens, ecological factors such as sun exposure associated with vitamin D deficiency may contribute to higher mutation rates and impaired repair of DNA(13). Also, environmental factors may affect gene expression through epigenetic change that increases the risk of autism. Therefore, attentions have recently begun to be paid to the examination of environmental factors associated with risk of autism (14).

In a recent animal study, Hao *et al*. (15)suggested that triclosan (TCS, 5-chloro-2-(2,4-dichloro phenoxy) phenol, an antimicrobial agent widely used in the personal care and household product, is a potential risk factor for developping autistic behaviors. While the United States Food and Drug Administration (FDA) banned TCS from use in soap products in 2016 and the European Union banned TCS from all human personal hygiene biocidal products in 2017, TCS remains allowed in toothpaste as this agent helps fight gingivitis(16). The potential mechanism causing autistic behaviors is through down-regulation of the cellular retinoic acid (RA) signaling(15), in which RA is also a morphogen molecule mediating neuron differentiation, synaptic plasticity, and tissue formation. This finding may provoke additional studies of this chemical on the risk of autism. It would be exciting but also a challenging task to establish a causal relationship between TCS and risk for autism in human populations. In using TCS to treat neural stem cells in vitro under different time points (3-24h) and dosage of concentrations(17), Park et al. show a dose-dependent increase in cell viability at 10 and 20 μM of concentraion for all time points but, interestingly, a decr-ease in cell viability at a dosage of 50 and 100 μM. They indicate that TCS can cause neurodegenerative effects on developping rat brains through the mechanisms involving ROS activation and apoptosis.

Hao *et al*. also suspect that TCS may alter the composition of the gut microbiome that could lead to the development of autistic behaviors. Altered microbiota composition caused by the use of antibiotics in early life has been pro-posed as a possible contributor in the etiology of ASD. There has been a paradoxical hypothesis that aminoglycoside antibiotics could trigger the autistic syndrome in susceptible infants by causing the stop codon read-through; whereas other antibiotics could improve the symptoms of ASD(18). A sibling-controlled analysis in a large population-based cohort sample suggests that antibiotics expo-sure in early life is not associated with ASD(19), and a systematic review also does not support that early life exposure to antibiotics is associated with risk of ASD(20).

Care should be taken in interpreting the findings from animal studies and cross-sectional association in human studies. Human beings are social and human populations are heterogeneous. The effect of TCS on autistic behaviors needs to be validated with a dose-response evidence in animals and human populations through epidemiological studies. Previous animal studies have shown that maternal immune activation (MIA) is a mechanism that link maternal infection to ASD. Prenatal viral infections have been associated with the risk of ASD(21). However, a meta-analysis of 15 studies that included more than 40,000 cases with ASD only showed a small effect of prenatal infections on the risk of autism (22) (OR=1.13; 95% confidence interval,1.03–1.23). This suggests that maternal infection only contributes a small proportion of risk to autism. Maternal

infection that causes peripheral immune dysregulation can begin in fetal development and continue to adulthood (23).

Concurrently in a recently published article, *Ou* et al. have examined two cohorts of autism cases and controls from distinct regions of China and identified multiple prenatal and perinatal factors including maternal environmental exposure, maternal infection, use of medication, experiencing a threatened abortion or induced abortion, associated with autism(24). These factors combined explain 9-15% of the variation in ASD in two cohorts of samples. In a case-control study of relatively common outcome (i.e., common disease), parameter estimates that measure the strength of association is not a good approximate to relative risk (RR) for a disease. The variation explained by those factors would generally be over-estimated. The causal relationship needs to be validated in population studies with an advanced design to determine a dose-response relationship.

However, measuring the dosage, duration and particularly how the timing of exposures relate to developmentally-sensitive windows in individuals, is not an easy task in humans. It may require a multidisciplinary effort to design a rigorous study and collect related data for a better understanding the role of genetic and environmental factors in particular the gene-enviromental interaction on the risk of developing ASD.

Fengyu Zhang, PhD, MS
Claudes Hughes, MD PhD

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