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A Self-Generated Environmental Factor as a Potential Contributor to Atypical Early Social Communication in Autism

Autism spectrum disorder (ASD) is defined by deficits in reciprocal social communication and interactions, as well as deficits in cognitive and behavioral flexibility. In the United States, the mean age for diagnosis of ASD is 4; diagnosis can be made as early as age 2. There is an intense interest in identifying much earlier signs of ASD because of the proven effectiveness of early intervention. Many infant behaviors, such as atypical cries (Esposito and Venuti, 2010), are being explored as such signs. However, the manner in which such early signs of ASD are causally involved in the developmental trajectory of cardinal symptoms of ASD remains unclear.

This picture is about to change, thanks to the development of mouse models of highly reliable genetic risk factors. Many cases of duplications or hemizygous deletions of kilo- to megabase chromosomal segments, termed copy number variants (CNVs), are robustly and reproducibly associated with high rates of ASD. For example, it has been known since 2001 that ASD is seen at high rates among carriers of 22q11.2 hemizygosity (Hiroi *et al,* 2013). Since 2007, other human CNVs have been similarly found to be associated with high rates of ASD.

Our group has altered copy numbers of small chromosomal segments within the 22q11.2 CNV and identified *Tbx1* as one of the 22q11.2 genes critical for various signs of ASD (Hiramoto *et al*, 2011; Hiroi *et al,* 2013). Moreover, we have developed and tested an experimental procedure to reliably assess the effects of typical and atypical vocal call sequences on maternal behavior. Our data showed that *Tbx1* heterozygosity caused atypical pup vocal call sequences, which then evoked less than optimal maternal care (Takahashi *et al*, 2016).

Less than optimal maternal care can be considered a 'self-generated environmental factor' of ASD, as it is induced, through atypical vocal sequences, by a genetic ASD risk carrier. Such an environmental factor clearly differs from those that unilaterally impact—and are passively perceived by—risk carriers, such as accidental environmental insults (eg, fetal and infant exposures to pesticides, viruses, and chemicals). The negative phenotypic loop between a risk carrier and its mother is likely to affect the developmental trajectory of ASD symptoms. Certainly, such a hypothesis is consistent with empirical evidence that parent-mediated interventions are effective in alleviating the ultimate degree of some ASD symptoms in humans (Green *et al*, 2010; Wetherby *et al,* 2014).

The Refrigerator Mother theory of autism claimed that autism was caused by a lack of maternal warmth. Our view does not attribute the causative event of ASD to mothers.

We submit that less than optimal maternal care is caused by atypical vocal signals of carriers of genetic risk factors and has a modulatory–not causative–impact on the developmental trajectory of severity of ASD symptoms. Our mouse-based hypothesis provides a novel potential mechanistic basis to improve our understanding of the developmental trajectory of ASD and innovative theoretical grounds to develop effective therapeutic interventions.

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