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Review

The Intersection of Genome, Epigenome and Social Experience in Autism: Exploring Modifiable Pathways for Intervention

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Abstract: The number of children diagnosed with autism spectrum disorder (ASD) has increased substantially over the past two decades with current research unable to fully account for this dramatic increase in prevalence. One explanation proposes that both intrinsic (e.g., genetic) and extrinsic (e.g., environmental) risk factors may be involved in the etiology of ASD. The goal of this review paper is to explore modifiable pathways for intervention in children at risk for ASD, specifically examining how early social experience may be correlated with epigenetic change in genes associated with autism. We present an innovative model which proposes that polygenic risk and social experience (via epigenetic mechanisms) may *both* contribute to the observed ASD phenotype. Previous research on genetic, environmental, and epigenetic mechanisms implicated in the etiology of ASD will be reviewed, with an emphasis on the oxytocin receptor gene, which is epigenetically altered by early social experience, plays a crucial role in mammalian social and cognitive development, and is associated with both genetic and epigenetic risk for ASD. Identifying intrinsic (e.g., genetic) and extrinsic (e.g., social experience) risk markers for ASD, a combination of which has not previously been examined, would transform our understanding of this condition, facilitate earlier identification of ASD risk, and guide early intervention efforts. This may have a far-reaching impact on individuals with ASD, their families, and society.

Keywords: autism; ASD; epigenetics; DNA methylation; genetics; oxytocin; social experience

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition which encompasses social communication deficits and repetitive/restricted behaviors and interests (APA, 2013). Diagnosis of ASD typically occurs around 2 to 3 years of age, when parents or healthcare professionals note developmental deficits, particularly in social communication and social-emotional reciprocity. The developmental trajectory of individuals diagnosed with ASD varies based on symptom severity and individual response to intervention. Regardless, individuals diagnosed with ASD will most likely continue to experience the associated symptoms to some extent throughout their lifespan and require ongoing intervention and assistance in several contexts (e.g., education, vocation, familial). The financial burden for the treatment and care of individuals with autism is estimated to be over $260 billion annually (Buescher, Cidav, Knapp, & Mandell, 2014). At present, treatment for ASD is limited to intensive behavioral interventions, and non-specific

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medications which are not effective against any of the core features of autism, including social communication difficulties and repetitive/restricted interests. The ability to treat or prevent these core symptoms is desperately inadequate, in large part because we do not fully understand the etiological and biological mechanisms underlying ASD. This, combined with the lifelong disabilities faced by many affected individuals and the impact on their families and society, highlights the urgent imperative to understand the etiology of autism.

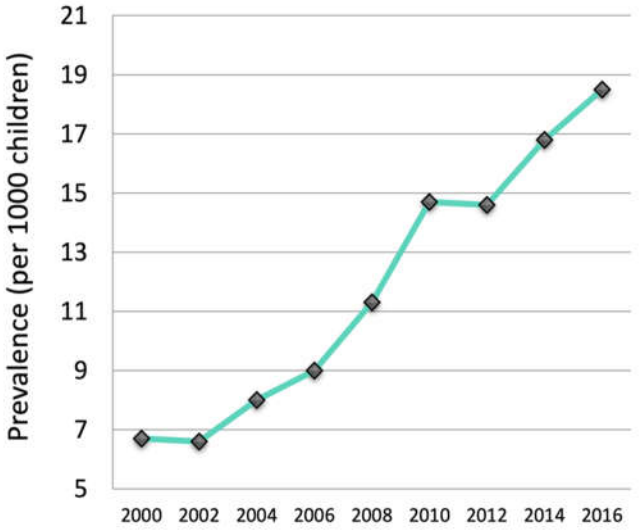

Figure 1. ASD prevalence in children 0-8 years from 2000 to 2016 (Maenner et al.,.

Notably, the number of children diagnosed with autism has soared over the past two decades (Figure 1) (Baio et al., 2018; Christensen et al., 2016; Maenner et al., 2020; Maenner et al., 2021). Recent estimates of prevalence in the U.S., based on representative population samples, found that 1 in 36 children and adolescents are diagnosed with ASD (Xu, Strathearn, Liu, & Bao, 2018). Potential explanations for the increased prevalence of ASD in recent years include improvements in diagnostic tools, changes to diagnostic criteria, and increased awareness about ASD, leading to more referrals for assessment. However, such explanations do not fully account for the increased prevalence, warranting consideration of other causal mechanisms that change over time, such as environmental influences (Weintraub, 2011).

Notably, research examining potentially modifiable environmental factors relevant to ASD, such as early social experience, is limited. This is despite the fact that social experience has a well-established impact on social and cognitive development, potentially via epigenetic mechanisms (i.e., structural modifications to DNA that result in alterations in gene expression). Rodent studies show that early social experience such as responsive tactile stimulation of rat pups alters DNA methylation (DNAm), affecting genes critical for social development, such as the oxytocin receptor gene (OXTR) located on chromosome 3p25 (Beery, McEwen, MacIsaac, Francis, & Kobor, 2016). In this case, DNAm downregulates gene expression and appears to alter social and cognitive development, although translational evidence for this mechanism is limited in human infants.

We have hypothesized that social experience may interact with genetic vulnerability to increase ASD risk via epigenetic mechanisms, notably DNAm (Strathearn, 2009). Over past decades, the pendulum of public and scientific opinion on the etiology of autism has swung between two extreme positions: 1) that autism is the result of a specific environmental factor or conditions, such as a "lack of maternal warmth" (Kanner, 1943); and 2) that autism is caused by a specific genetic abnormality, spawning a search for the "autism gene." The evidence to date has strongly refuted both extreme positions. However, few,

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if any, previous studies have examined how early social experience may interact with genetic factors to impact the development of autistic-like behaviors.

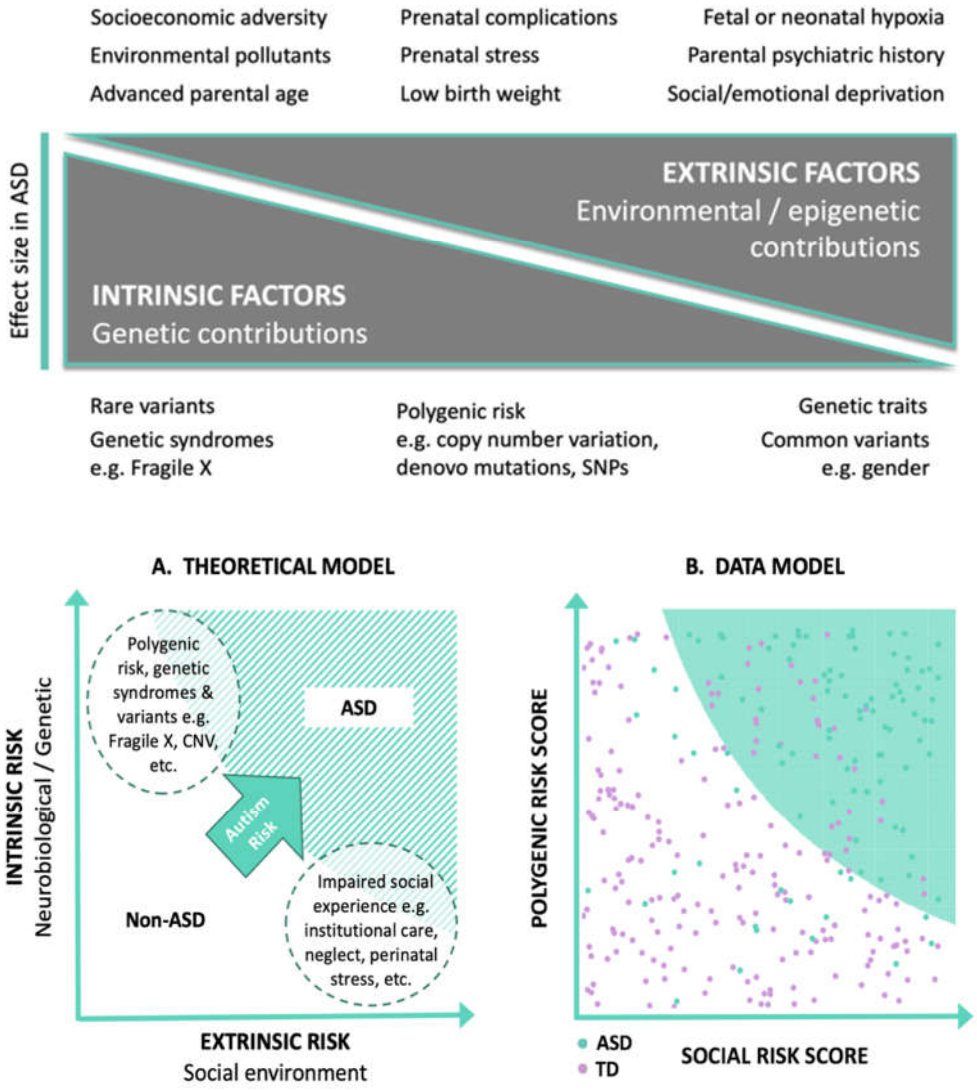

Figure 2. Model of intrinsic and extrinsic risk factors for autism. **A.** Theoretical model of how polygenic risk scores and social risk may predict the development of autism, with examples given from each axis. **B.** Simulated model of intrinsic and extrinsic risk scores for autism based on multiplicative interaction effects, along with unknown contributions to risk. For illustration purposes, half of the autism liability derives from the combination of genetic and environmental factors, while unknown causes account for the other half. The shaded green area represents an estimate of the region where children are at high risk for autism, based on an analysis of the simulated data.

Currently, there are models which propose that both intrinsic (e.g., genetic) and extrinsic (e.g., environmental) risk factors may be involved in the etiology of autism (Geschwind, 2011; Jiang et al., 2004). Specifically, genetic factors may alter the susceptibility for developing ASD, while environmental factors may lead to epigenetic changes which regulate gene expression and contribute to ASD symptomology (Figure 2A). The goal of this review paper is to explore modifiable pathways for intervention in children who may be diagnosed with ASD, specifically examining how early social experience may lead to epigenetic changes in genes associated with autism. We present an innovative model which proposes that polygenic risk and social experience may both contribute to the observed autism phenotype through epigenetic mechanisms (Figure 2B).

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2. Genetic Factors in ASD

Estimates of heritability for autism range from 65 to 90%, with the most recent and largest international study estimating ~80% (Bai et al., 2019). A meta-analysis of twin studies found an almost perfect correlation for monozygotic twins and the occurrence of ASD (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016). For dizygotic twins, however, the correlation was only moderate. Overall, the meta-analytic heritability estimates were between 64-91%, with shared environmental effects being significant when prevalence rates were low. While heritability estimates are helpful in quantifying genetic contribution to etiology, identification of specific variants that contribute to the observed phenotype is key to elucidating mechanisms and identifying biomarkers with potential risk prediction utility.

Significant progress has been made in identifying genetic variants. Several hundred variants have been associated with ASD, including many single-nucleotide variants (SNVs; one nucleotide is substituted for another) and copy number variants (CNVs; duplication or deletion that changes the number of copies of a particular segment of DNA) (Ramaswami & Geschwind, 2018). While many genetic variants are inherited, studies have shown an increase in rare *de novo* genetic variants among individuals diagnosed with ASD (Waye & Cheng, 2018; Woodbury-Smith & Scherer, 2018). In fact, *de novo* CNVs occur four times as frequently in ASD children compared to their neurotypical siblings (Ramaswami & Geschwind, 2018). Several specific rare genetic variants have been strongly associated with ASD risk, such as mutations in *TSC1* and *TSC2* (which leads to tuberous sclerosis complex) and the *FMR1* gene variant found in Fragile X Syndrome (Varghese et al., 2017). Rare variants with relatively large effect sizes have been identified in up to 15% of ASD cases, with the variants implicating several biologic processes, including epigenetic processing, signaling pathways, and synaptic function (Krumm, O'Roak, Shendure, & Eichler, 2014; Sanders et al., 2015). In more recent years, common genetic risks for ASD have emerged (Grove et al., 2019) through the Psychiatric Genetics Consortium, Autism Workgroup (PGC-AUT), in large part due to the addition of tens of thousands of samples from the Danish iPSYCH study (iPSYCH; https://ipsych.dk/en/about-ipsych). As the world-wide sample size for ASD continues to grow, additional common variants that contribute to risk will likely be discovered.

Thus, genetic factors clearly contribute to the development of autism (Figure 2). However, this does *not* equate with genetic causation, nor exclude the possibility of environmental effects. Although ASD has a high heritability estimate, the statistical models used in heritability studies often assume that genes do not interact with the environment, or with other genes, to influence phenotype, which is not the case. Additionally, while an increasing number of genetic variants associated with autism have been identified, the effect sizes are invariably small, and any individual variant is insufficient to explain the heritability estimates (Owen & Williams, 2021). This has led to consideration of the combined effect of genetic variants using a polygenic risk score for autism – which sums individual common variant risk effects into an aggregate genome-wide risk value – and through the incorporation of both common and rare genetic risk variants in studies (Grove et al., 2019; Guo et al., 2017). Nevertheless, focusing solely on the genetic contributions of autism precludes the possibility of intervening and potentially preventing adverse consequences due to modifiable factors.

3. Environmental Factors in ASD

An important environmental factor known to have a profound effect on social and cognitive development is social experience, as demonstrated by decades of animal research (Caldji et al., 1998; F. Champagne & Meaney, 2001; F. A. Champagne & Meaney, 2007; D. Francis, Diorio, Liu, & Meaney, 1999; Ladd et al., 2000; Meaney, 2001; I. C. G. Weaver et al., 2004) and human experimental and epidemiological studies (Bick & Nelson, 2017; Kuhl, 2004; Strathearn et al., 2020). Both Dawson (2008) and Schultz (2005) have hypothesized that basic deficits in social perception and experience may underlie many other developmental and behavioral abnormalities of ASD, and that a set of defining

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experiences early in life (or lack thereof) may adversely affect the development of multiple cascading neural pathways. Just as visual deprivation during a critical period of development may result in permanent disruption of the visual pathways and long-term visual impairment (Wiesel & Hubel, 1965), restricted social experience—either extrinsically or intrinsically derived—may lead to long-lasting impairment in social development. A child's social experience may be affected by a variety of factors, ranging from perinatal stress and premature birth to socioeconomic adversity and parental psychopathology (Figure 2).

Prior studies have demonstrated associations between early social experience and the development of social communicative abilities in both typical and atypical populations. A prospective study of infant siblings of children with ASD, showed links between language exposure at home during the first year of life and subsequent language development in toddlers now diagnosed with ASD (Swanson et al., 2019). Specific characteristics have also been noted in children at-risk of ASD, based on videotaped behavior and naturalistic recording of vocalizations and language exposure, including an impaired ability to respond to a caregiver's social bids (Gangi, Ibanez, & Messinger, 2014; Swanson et al., 2018). Infants who are later diagnosed with autism previously exhibited a reduced frequency of vocalizing with speech sounds (consonant-vowel syllables) (Patten et al., 2014; Plumb & Wetherby, 2013). Likewise, toddlers later diagnosed with ASD used fewer deictic gestures (show/give/point) and initiated joint attention at a lower rate than typically developing toddlers (Shumway & Wetherby, 2009). Each of these developmental characteristics may be causally related to early social experience.

One extreme human example of the potential impact of impaired social experience on the development of ASD-like behaviors is with Romanian orphans who were exposed to severe physical and social deprivation, then later adopted into the U.K. (Rutter et al., 1999). At age 4, over 10% these children were clinically indistinguishable from children with "typical" ASD, and almost 20% had ASD-like features. Furthermore, their symptom severity was directly correlated with the length of time spent in the institution (Rutter et al., 2007). A subsequent study confirmed that children raised in institutions, compared to non-institutional family-centered care, were at increased risk of developing ASD and displaying significant deficits in social communication. Children randomly assigned to live with available foster care families showed an intermediate risk compared with children living with their natural family (Levin, Fox, Zeanah, & Nelson, 2015).

Numerous studies have also shown that ASD interventions focusing on parenting are more likely to produce sustained improvements in child behavior and social development (Lindgren et al., 2016; Pickles et al., 2016; Steiner, Koegel, Koegel, & Ence, 2012; B. Tonge, Brereton, Kiomall, Mackinnon, & Rinehart, 2014; B. J. Tonge, Bull, Brereton, & Wilson, 2014). In fact, randomized trials of parent-mediated interventions for children at high familial risk for ASD revealed reductions in ASD symptoms persisting up to three years post-intervention (Green et al., 2017; Whitehouse et al., 2021).

4. Epigenetics, Social Experience, and ASD

Given the evidence that genetics and environment both play a role in the etiology of ASD, the study of epigenetic mechanisms may be particularly relevant, including histone modifications, micro-RNA (miRNA), and DNA methylation (DNAm) (Yoon, Choi, Lee, & Do, 2020). The most studied epigenetic mechanism is DNAm, largely because it is relatively simple to assay, cost-effective, and can be completed using a variety of biological samples with minimal biological material required. DNA loci containing cytosine (C) and guanine (G) nucleotides linked by a phosphate bond (p) are termed CpG sites and labelled in the genome using specific loci IDs and positions (see Table 1). When methylated (by adding a methyl group to the cytosine nucleotide), gene expression and cellular function may be altered.

There is broad evidence supporting DNAm differences in ASD, utilizing both blood and brain tissue (Andrews et al., 2017; Ladd-Acosta et al., 2014). A meta-analysis of post-

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diagnosis case-control blood samples from 796 ASD cases and 858 controls, aged 5-17 years, identified 7 methylation differences, with suggestive ASD association p-values (Table 1, Set B). Several of these loci had a similar direction and an even greater effect size in the brain (Andrews et al., 2018). Another study identified 20 loci in Danish newborn dried blood spots with differential methylation patterns seen in children later diagnosed with ASD (Table 1, Set A) (Hannon et al., 2018). While some DNAm loci remain unchanged between birth and later ASD diagnosis (Hannon et al., 2018), it is unknown whether these 27 ASD-related DNAm profiles change between birth and ASD diagnosis, and whether these changes are associated with social experience. Broadly, the genes identified in this latter study are involved in methylation machinery, hippocampal plasticity, epigenetic modulation of social and motivational behavior, neural cell differentiation, glucocorticoid metabolism, and vasopressin metabolism (Carelli et al., 2019; Henriquez et al., 2013; Johnstone et al., 2018; Kundakovic et al., 2014; Lester et al., 2018; Siu & Weksberg, 2017; I. C. Weaver et al., 2004).

The oxytocin receptor gene (OXTR in humans, Oxtr in rodents) is also of particular interest, given that its substrate, oxytocin, is a neuropeptide implicated in social salience, including eye gaze, empathy, and pair-bonding behavior (Mitre, Minder, Morina, Chao, & Froemke, 2018). Oxytocin and OXTR are programmed by early life experience, influence patterns of eye gaze and face perception, and play crucial roles in mammalian social development. Moreover, there are several DNAm sites in OXTR associated with ASD in humans. Brain Oxtr expression in rodents appears to be programmed by early life experience, with decreased expression seen in the blood and brains of animals who receive lower levels of social experience in infancy (Beery et al., 2016; Francis, Champagne, & Meaney, 2000), and Oxtr knockout mice have impaired social memory and recognition (Lee, Caldwell, Macbeth, Tolu, & Young, 2008) and impaired mother-offspring interactions (Nishimori et al., 2008). In addition, OXTR hypermethylation has been associated with suppressed gene expression (Kusui et al., 2001), reduced circulating oxytocin (Dadds et al., 2014), and decreased OXTR expression in the temporal cortex of the brain of ASD vs. non-ASD controls (Yuksel, Yuceturk, Karatas, Ozen, & Dogangun, 2016; Gregory et al., 2009) (Table 1, Set C). More recently, a human longitudinal study showed that decreased social experience during infancy predicted increased methylation in a conserved regulatory site of the OXTR gene one year later, and that increased OXTR methylation at 18 months reflected differences in child behavior relevant to ASD (Krol, Puglia, Morris, Connelly, & Grossmann, 2019). Thus, early life social experience may modify epigenetic markers affecting gene expression in the brain and social behaviors relevant to ASD .

5. The Intersection of Genome and Epigenome in ASD

Understanding cross-omics relationships, e.g. how genetic variation is related to gene expression, DNAm, or protein levels can provide important biologic insights into how genetic risk variants manifest into disease. With the emergence of cost-efficient genome-scale measurement tools, many studies have now measured multiple -omics from the same participants and have shown that gene expression levels can be controlled by genetic variation, including in a tissue specific manner . Single nuleotide polymorphisms (SNPs) that control gene expression levels are called expression quantitative trait loci (eQTLs). Similarly, SNPs can also regulate DNAm levels; these are commonly referred to as meQTLs. These relationships can occur in -cis, i.e. in close genomic proximity, or in -trans, where the SNP and the gene whose expression or methylation that it regulates is very far away in linear distance or even on a different chromosome.

ASD genetic risk variants located outside of protein coding regions of genes are postulated to play an important role in gene regulation. Evaluating whether ASD genetic variants regulate gene expression or DNAm levels, and in which cell types, can provide information on biologic mechanisms that contribute to ASD etiology and identify potential gene/pathway targets for treatment or intervention purposes (Pavlides et al., 2016; Zhu et al., 2016). Studies using eQTL and meQTL maps have shown ASD risk

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variants, discovered via GWAS, are enriched for being eQTLs (Cheng, Quinn, & Weiss, 2013; Davis et al., 2012) and meQTLs (Andrews et al., 2017) when compared to non-ASD SNPs with similar properties, particularly in neurodevelopmentally relevant tissue types such as fetal brain. Additionally, they have identified potential regulatory gene targets of ASD SNPs that would not have been otherwise identified when considering genomic location of the SNP alone.

Integration of genome and epigenome data has provided insights into ASD etiology and may inform future avenues of treatment research. It is also worth investigating whether DNAm and expression patterns at loci targeted by genetic variants are also susceptible to environmental exposures, including ASD risk factors, which could implicate shared pathways and targets for different risk factors and/or potential mechanisms for gene-environment interactions. Another important line of future research will be to expand integration of genetic data with other omics measures including the proteome, metabolome, and microbiome, among others. Finally, it is worth considering how relationships between the genome and epigenome can be used for predictive biomarker purposes, even if they are not part of the causal mechanistic pathway for ASD. While the proportion of phenotypic variance in a population that can be explained by genetic variants, in aggregate, is often very small, there is evidence that including epigenetic measures in predictive models can improve these estimates (McCartney et al., 2018).

Table 1. Proposed DNA methylation loci associated with the pathogenesis of autism. Set A involves differentially methylated loci at birth; Set B at time of ASD diagnosis; and Set C involving OXTR promoter region.

Study	Nearest Gene	Chromosome	CpG Loci ID	Position
A. Hannon *et al* (2018) - Dried blood spots - N=1263 - Infants at birth, who developed ASD	RALY	20	cg12699865	32583031
		16	cg03697766	54848022
	UNC84A	7	cg25203085	887678
		5	cg20712043	16392700
	TG	8	cg04918350	134124199
		6	cg21986027	169238138
	TRIM2	4	cg14001992	154073813
	RD3	1	cg00692367	154073813
		1	cg16254267	1073529
	C2orf85	2	cg03270969	242813189
	LHCGR	2	cg06995408	48977089
	PAG1	8	cg09973676	82006417
	ZCCHC24	10	cg25485956	81146099
		14	cg23256480	93252030
	KLF8	X	cg22829182	56258808
	CCDC147	10	cg02803139	106113391
	LOC100128573	19	cg03260991	7539710
		10	cg04089434	94516971
	KDR	4	cg02723107	55987799
	KCNJ10	1	cg20064848	160037877
B. Andrews *et al* (2018) - Blood - N=968 - ASD Children/ adolescents	CENPM	22	cg21151899	42337657
	FENDRR	16	cg03731974	86531598
	SNRNP200	2	cg09962502	96971189
	PGLYRP4	1	cg01798266	1.53E+08
	EZH1	17	cg01716316	40897182
	DIO3	14	cg16234726	1.02E+08
	CCDC181	1	cg09671955	1.69E+08
C. Gregory *et al* (2009) - Blood (PBMC) - N=40 - ASD	OXTR	3	CpG-924, Intron 3, MT2	8769047
				8769121
				8769146

6. Conclusion

Recognizing and understanding the significance of predictive markers for autism has been a vexing challenge in ASD research over the past two decades, especially in view of its dramatically increasing prevalence. Limited validity and reproducibility of candidate gene approaches linking specific polymorphisms to clinical phenotypes have necessitated a change in emphasis to genome-wide and methylation array approaches. In addition, understanding the potential interaction between polygenic risk and social experience in the development of ASD has been hampered by the lack of large prospective studies drawn from unbiased community samples *without* ASD-affected family members. Although numerous studies have examined genetic and environmental factors contributing to ASD risk, additional studies are needed to look at how epigenetic mechanisms may mediate their effects on ASD risk, using a prospective design and eliminating the need to rely on infant siblings of children already diagnosed with ASD. Identifying intrinsic (e.g., genetic) and extrinsic (e.g., social experience) risk markers for ASD, a combination of which has not previously been examined, would transform our understanding of this condition, facilitate earlier identification of ASD risk, and guide early intervention efforts. This may have a far-reaching impact on individuals with ASD, their families, and society.

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Conflicts of Interest: Dr. Ladd-Acosta is an Associate Professor in the Department of Epidemiology at the Johns Hopkins University Bloomberg School of Public Health and is engaged in this research as a private consultant or advisor and not in her capacity as a Johns Hopkins faculty member. She was compensated for these services by the University of Iowa in the form of income.

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