Chapter 3: Genetic and Environmental Factors

What Are the Genetic and Environmental Factors that Contribute to Autism?

Introduction

Aspirational Goal: Discover genetic and environmental factors that influence the development of autism in order to better inform diagnosis and interventions to improve the quality of life for people on the autism spectrum.

Over the past 10 years, there have been substantial advances in the understanding of factors that contribute to a diagnosis of autism spectrum disorder. There has been an increased appreciation of the incredible complexity and interplay of genetic and environmental factors in the development of autism. Studies have highlighted the fact that environmental factors can affect different people in markedly different ways depending on the individual's genetic background. Therefore, significant attention is being devoted to understanding these "gene by environment" interactions. This chapter emphasizes the desire to understand the genetic and environmental factors that influence the presentation and trajectory of autism across the full heterogeneity of the spectrum. These go beyond the core characteristics of autism to include co-occurring physical and mental health conditions that can cause mild to severe challenges. There is critical need to understand the causes of these co-occurring conditions and identify interventions that can improve outcomes.

The neurodiversity movement has had a great impact on the work of the IACC and on the autism community as a whole. Prevention of autism was a focus of scientific research in the 1990s and early 2000s. In more recent years, however, many advocates voiced concerns about the origins of causation research in prevention of autism and that research on factors that contribute to autism causation could ultimately lead to eugenics or other harms of autistic people. During this time, the neurodiversity movement has fostered a new appreciation of the role and value of autistic and other neurodiverse people as an integral part of society and has called for a change from research to prevent autism to research to support the health and well-being of autistic people. Over time, the *IACC Strategic Plan* has reflected this shift from a prevention focus to a focus on acceptance of autism and improving quality of life and outcomes.

In the *2021-2022 IACC Strategic Plan*, the focus of the IACC's recommendations is to encourage research that will improve and contribute to the highest quality of life for autistic people, and including acceptance and understanding of autism, and options for addressing issues that cause challenges for autistic people, such as co-occurring physical and mental health conditions. It is also acknowledged that the term "risk factor" is inherently stigmatizing and implies that autism is a negative outcome to be avoided. Though "risk factor" is a technical term still used in the research literature, in the *IACC Strategic Plan*, contributing factors are described using neutral language. Over the past 10 years, there has been

an increased sensitivity to these concerns among funders, researchers, and other stakeholders, and this is reflected in the evolution of this chapter across several editions of the *Strategic Plan*. Still, it is important to acknowledge that understanding the genetic and environmental factors that influence autism is an important avenue of research. Findings from these studies may be useful in identifying biomarkers that will improve screening and diagnosis as well as developing personalized interventions. This line of research can also provide more basic information on the development and function of the brain that would broadly benefit neuroscience research and research on related disabilities and conditions.

Genetic Factors

Studies of the human genome have significantly advanced the understanding of genetic factors that influence the development of autism. Similar to other common mental health conditions, the contributing genetic variations are complex, involving both common and rare forms of genetic variation[1]. Modifications in more than 100 genes are now known to increase the probability of an autism diagnosis[2]. However, it is important to note that it is unlikely that these genes are specific to autism; rather they are believed to impact the core features of autism to varying degrees and are, in many cases, are implicated in additional genetic, psychiatric, or neurodevelopmental conditions[3,4,5]. The types of genetic variations that are linked to autism are wide-ranging, including de novo (new, spontaneous, non-inherited) and inherited mutations. Protein disrupting genetic variants occur in 27% of individuals on the autism spectrum and are associated with co-occurring conditions, including intellectual disability, learning disabilities, and epilepsy[6]. Some ASD diagnoses can be linked to a mutation in a single gene (syndromic autism), while differences in multiple genes in the same individual (polygenic variation) may account for the greatest proportion of genetic influence[7,8]. Advances in sequencing methods have greatly accelerated progress in identifying genetic factors. A critical next step will be to integrate understanding of rare variants with large effects with more common polygenic risk factors to more accurately identify autism on an individual level.

Autism is highly heritable, in that up to 60-90% of autism cases are linked to known or unknown genetic factors[9]. Siblings of children with autism are 10-20 times more likely to receive an autism diagnosis themselves than non-siblings[10,11,12]. Several studies of autism in twins have sought to estimate the relative influence of genes and the environment in autism[13]. Most of these studies have identified substantial contributions of both types of genetic and environmental factors, although the proportions of the two factors and interpretations have varied substantially. A recent study found that while twins often shared an autism diagnosis, the characteristics vary from one twin to another, suggesting a significant influence of non-shared environmental factors[14].

In some cases, specific genetic mutations have been linked with particular phenotypes, or outward characteristics. Patterns of behavior or co-occurring conditions linked to sub-phenotypes can prove helpful for establishing guidelines of care for clinicians. While major advances have been made through the understanding of how genes contribute to autism, gaps exist in our understanding of the contribution of regulatory and other noncoding (non-gene) regions of the genetic code to the likelihood of developing autism.

Genetic Overlap with Other Conditions

Neuropsychiatric and developmental conditions share many genetic factors, and this varies depending on the specific conditions being compared[15,16]. Autism shares common genetic variations with neuropsychiatric conditions such as schizophrenia[17,18], and autism is sometimes a feature of other neurodevelopmental syndromes such as Fragile X syndrome, Rett syndrome, tuberous sclerosis, and Phelan McDermid syndrome[19,20,21,22]. The common, polygenic influences on autism are similarly associated with multiple phenotypic outcomes (different combinations of genetic mutations can lead to different neuropsychiatric and developmental conditions). In recent studies, researchers found significant genetic correlations between autism and several other traits and conditions including schizophrenia, major depression, and measures of cognitive ability such as educational attainment[23]. In the future, it will be important to further explore commonalities with other mental health conditions.

Genetic Basis for Sex Differences in Autism

The most recent prevalence data from the CDC suggests that autism 4.3 times more prevalent in males vs. females[24]; other estimates have consistently estimated that males are 3-4 times more likely to be diagnosed with autism than females[25]. While there is evidence that the actual male:female ratio is lower, it is clear that there are often differences in the presentation of autism in males vs. females and that this may result in underdiagnosis of females. Differences in autism between males and females are likely due to a combination of social and biological factors. Researchers have therefore sought to identify genetic factors that may contribute to the difference in prevalence.

One hypothesis proposed to explain the difference in prevalence is the “female protective effect” (FPE), which suggests that females are biologically 'protected' from autism such that, on average, a greater number of genetic factors is necessary for a female to display autism traits. There has been some research that supports the FPE concept[26,27,28], but a recent study calls the hypothesis into question. Researchers analyzing health records from a population-wide registry found that the unaffected sisters of autistic individuals were just as likely to have autistic children as the unaffected brothers of autistic individuals[29]. This study demonstrates that a potential FPE can not fully account for the sex differences in prevalence. It is therefore critical to continue exploring potential genetic contributors to autism that are differentially influenced by sex[30]. It is also necessary to consider the non-genetic causes that may influence diagnosis rates, including increased social masking behaviors in females and male bias in diagnostic instruments.

Environmental Factors

In addition to genetics studies, research on potential environmental factors reflect the current understanding that multiple types of factors can influence autism. In this *Strategic Plan*, it is advantageous for the IACC to adopt a broad definition of studies on "environment" as encompassing research on all potentially non-heritable influences. This includes studies of environmental exposures such as pesticides, hormone disrupting and other industrial chemicals, pharmaceuticals, heavy metals, infectious agents, or dietary factors, as well as other factors, such as parental age, maternal medical conditions, preterm birth or birth complications, and time between pregnancies[31,32,33,34,35,36]. Some of these "environmental" factors might themselves be genetically influenced, while others might be mediating the effects of environmental exposures.

Research on environmental contributors to ASD should routinely collect and make use of data on specific traits related to autism and its co-occurring conditions, including the variation in autism-related characteristics when appropriate. As linkages between exposures and specific characteristics are revealed, public health strategies can be adjusted to help people avoid exposures that are linked to poor outcomes and increase modifiable factors that confer resilience or improve quality of life. Additionally, improved understanding of what role environmental factors play in autism phenotypes (including risk for co-occurring conditions) may eventually inform strategies for identifying children in need of specific types of early intervention services.

While the number of autism epidemiology studies and the resulting data are growing, most potential environmental factors have not been investigated sufficiently to draw firm conclusions[37]. The limitations inherent to observational studies mean that multiple studies in different populations and settings, with high-quality measures of exposure and adequate controls, are needed to reconcile disparate findings and establish robust linkages of an environmental exposure to autism likelihood. The assumption that many different factors, each with modest effect, will contribute to autism means that large sample sizes may be needed to detect associations with exposure, especially for those exposures with low prevalence. In addition, more research is needed to understand if environmental exposures during specific vulnerable periods prior to conception, during pregnancy, or in the early postnatal period are linked to ASD, co-occurring conditions, and/or differences in characteristics and outcomes.

Exposure Science

One of the most significant obstacles facing epidemiologic studies of environmental contributors to autism is exposure assessment. In many studies, exposure measures are not readily available for very early developmental periods and rely on indirect methods (e.g., participant recall of prior exposures), or utilize one or two biologic measurements of compounds with very short half-lives. Direct exposure assessment, such as through personal monitoring or use of an adequate time-course of exposure biomarkers, is expensive and burdensome for participants. Consequently, deep characterization of exposure during relevant time periods is typically limited to studies with small numbers of participants, yielding low power.

In response to these challenges, researchers have developed methods to examine the exposome, or the cumulative exposures experienced during an individual's lifespan[38,39,40]. In addition to the universe of external environmental factors, the exposome concept can be extended to include endogenous biomarkers of exposure response – internal exposures that originate from metabolism and other cellular processes – as well as more general external factors that constitute social determinants of health. In combination with other "-omics" approaches, such as metabolomics, researchers have been able to identify biomarkers associated with autism by analyzing hair, teeth, or blood serum of individuals with autism and typically developing controls[41,42,43,44,45,46]. Similar to genomics, exposome studies are well-suited to help understand interactions among multiple exposures and to uncover novel environmental factors. Advances in this field can also lead to development of personalized interventions. However, it will be challenging to capture and integrate many measures over time. Strategies to address this include the use of personal sensors and mobile devices. Refinement of more targeted, conventional exposure assessment tools will also be necessary to fully characterize the exposome[47].

Gene-Environment Interactions

There is general agreement that both environment and genetics contribute to the development and trajectory of autism. Recent research studies have sought to identify gene-environment interactions[48] in order to understand how these multiple factors may influence each other and in turn influence neurodevelopment[49]. While many studies have made progress in understanding the interactions between one or a few genes and environmental factors, it will be critical in the future to integrate data on larger networks of genes and exposures.

Ideally, researchers could leverage existing datasets in order to undertake these studies. However, many large ASD genetic collections include minimal or no exposure information. On the other hand, studies focused on environmental factors often feature deep exposure assessment and have incorporated some genetic information, but smaller sample sizes limit the power of gene-environment interaction analyses. Therefore, a concerted effort is needed to enrich existing, ongoing ASD studies by adding genetic data collection to environmental studies and exposure measures to genetic studies. Availability of low-burden exposure measures that can be incorporated in large-scale genetic studies, perhaps leveraging innovations in exposomics, metabolomics, or epigenomics, is a high priority. Once these data exist in concert in large sample sets, new statistical and analytic approaches for gene-environment discovery in human population research can be applied[50]. Polygenic risk scores (the cumulative measure of the influence of multiple genes) have seen increasing use in complex disease studies and can yield improved efficiency for detecting interaction of genetic factors with candidate environmental exposures. The construction of a "polyenvironment" score, analogous to a polygenic risk score, could be explored to summarize information from several exposures thought to be acting through common mechanisms for use in genetic/genomic studies. Other approaches might include measures of genomic instability such as global copy number burden, used in two different gene-environment interaction studies[51,52].

Increasing knowledge of genetics has led scientists to understand gene pathways that affect neural circuits rather than single genes acting in isolation. Early studies have demonstrated the convergence of genetic influences and environmental factors in the activity of these different gene pathways, providing evidence that genes and the environment might work synergistically, rather than additively[53]. Studies that move beyond identification of genetic and environmental factors to reveal functional biological consequences associated with these factors are a priority. Epigenomics, metabolomics, transcriptomics, and proteomics can provide useful functional readouts for this purpose.

Model systems provide an attractive means for understanding biological mechanisms that underlie associations observed in human studies. Human induced pluripotent stem cells (hiPSCs) generated from autistic individuals with a known genetic background are being used increasingly to study autism[54]. These provide a unique opportunity to assess susceptibility of early developmental processes to environmental influences in the context of defined genetic risk[55]. Brain organoids, which are hiPSCs that have self-organized to form three-dimensional, functional structures in a petri dish, also provide potential for use as a model to further understanding of gene-environment interactions in syndromic subgroups of autism[56]. There are a few reports of screening or computational approaches used to identify possible environmental exposures that could be priorities for pursuit in human

studies[57,58]. Additional efforts that bring together interdisciplinary teams to facilitate integrative analyses and bidirectional flow of clues from human observational studies to laboratory-based experiments in model systems are warranted.

Epigenetics

Identifying how a person's genes can influence how the body responds to exposures is critical for interpretation of ASD-exposure associations. Regulation of gene expression, commonly referred to as epigenetics, is a key component in the response to genetic variation and environmental exposures[59,60]. Epigenetic mechanisms involve molecules that can alter the activity of genes within a person's DNA, either enhancing activity, silencing the gene, or changing the kind of protein that results from the gene's activity. Multiple lines of evidence implicate epigenetic changes in development of autism, and several known genetic disorders with autism-related presentation, such as Fragile X and Angelman syndrome, have established epigenetic mechanisms. A recent study has characterized how epigenetics influences patterns of variation in autism and other mental health conditions[61]. Results from rare-variant ASD genetic discoveries point to remodeling of DNA as a shared pathway in ASD genetics. Additionally, a significant body of work demonstrates that environmental chemicals can alter epigenetic factors, and these alterations have been linked to changes in gene expression and a range of behavioral phenotypes[62,63,64].

Autism research that integrates epigenetic, exposure, and phenotype data in the same population are a priority. Studies that identify exposure-induced impacts on a full range of epigenomic mechanisms and that determine their relevance to autism are needed. Finally, research to understand how exposure-induced epigenomic changes may transmit autism across generations is warranted.

Other Physiological Contributors

Outside of the nervous system, several other physiological systems have been implicated in autism (discussed further in Chapter 2). For example, several recent studies have illuminated the influence of immune differences in autism[65]; researchers are now exploring how a range of environmental exposures may contribute to the immune alterations observed in autism, some of which are detectable at birth[66]. Similarly, the endocrine system is another promising area of inquiry. The established role of hormonal systems in brain development, the male-to-female ratio of ASD diagnoses, and a growing recognition that many environmental chemicals act as human hormone mimics (known endocrine disrupting chemicals or EDCs) sets the stage for investigations exploring possible links between autism and EDCs[67]. Further work elucidating connections across metabolic, hormonal, and central nervous systems in the context of EDCs is needed.

The microbiome (the combined genetic material of the microorganisms in the body) represents a third priority area of inquiry. There is increasing evidence for links between the gut microbiome, brain, and behavioral phenotypes relevant to autism[68,69,70]. The microbiome is also emerging as an important component of response to environmental exposure. Studies have demonstrated persistent changes in the function of the microbiome after exposure to immune activation and environmental chemicals[71,72], particularly during early life when the microbiome is being colonized. A role for the microbiome in metabolism of environmental chemicals has also been established[73,74]. This means that

variations among individuals in microbiome composition can differentially regulate the metabolism of environmental factors, potentially contributing to variations in the presentation of autism. Small clinical studies using antibiotics or microbiome transplant support a potential role for microbial imbalance in contributing to the autism phenotypes. Continued exploration of microbiome function following environmental exposures should further elucidate their influence on autism.

Studies in Diverse Populations

Under-represented minority communities and low-income communities often face disproportionate exposure to harmful environmental exposures[75,76,77]. Additional attention is needed to ensure that these populations are represented in research on environmental contributors to autism. Ultimately, it will be critical for disparities in environmental factor exposure to be addressed.

Studies that examine environmental factors within sex-specific subgroups are especially important. However, given the lower ASD diagnosis rate in females, many studies to date have not had a sufficient sample of females to conduct such analyses. Thus, additional efforts are needed to increase representation of females in autism research studies to enable meaningful analyses of sex-specific differences and the role of both genetic and environmental factors in affecting those differences. The Environmental Influences on Children's Health Outcomes (ECHO) initiative of the National Institutes of Health is combining data from more than 60 cohorts comprising over 100,000 people, including approximately 61,000 children. Although the extent of ASD-related measures that are, or will be, included in ECHO has not yet been established, this initiative represents an exceptional opportunity to study ASD-related traits in large and diverse populations.

Resources to Accelerate Research on Genetic and Environmental Factors

Large-Scale Genetics Studies

Studies of the genetic architecture of ASD have resulted in the appreciation that much larger groups of subjects are needed to fully understand its complexity. In the last decade, several large-scale projects have been initiated. Large-scale efforts include the MSSNG project and database (funded by Autism Speaks), which provides access to genome sequences from over 11,500 individuals on the autism spectrum for research, and the SPARK study (funded by the Simons Foundation), which has collected exomes sequences from over 100,000 autistic individuals and 175,000 family members. These studies are contributing to knowledge of additional autism genetics. The Autism Sequencing Consortium (funded mainly by NIH) recently published results from their exome sequencing study of nearly 12,000 autistic individuals; they have also developed a gene browser that displays variant and gene-level data from their most recent analysis[78]. Other large genomics efforts, such as the Psychiatric Genomics Consortium, are looking more broadly at several mental health conditions, including autism. Work from this large international collaboration has identified five individual genetic variants that are associated with autism, as well as quantitative and qualitative polygenic heterogeneity across autism subtypes[79].

Broad Data Access and Resource Sharing

As the studies focusing on autism environmental factors amass increasing amounts of data attention to broad data access and sharing becomes critical for enabling reuse and extracting the maximal value from the data that have been collected. Combining data across observational studies can yield increased power and strengthen generalizability, yet the lack of standardization in of the types of exposure measures used creates challenges for both meta-analyses and pooled analyses of primary data. Consideration of privacy and consent issues in environmental health data is needed to ensure the development and implementation of policies that protect privacy while ensuring the value of shared data. The development of consensus data standards will make it possible for investigators to include genetic data in studies of environmental factors and vice versa. With regards to mechanistic tools, new models of autism, especially those with distinguishing genetic mutations of interest, should be made widely accessible to researchers. Finally, efforts must be put into the developing analytic approaches needed to help researchers mine data from large or aggregated data sources. Efforts that encourage methodological development as well as bioinformatics implementation and secondary data analysis funding will be necessary.

Interdisciplinary Training and Career Development

The workforce needs related to genomics and environmental research in ASD align with an increasing recognition that solving complex questions will require team science approaches. Programs and opportunities that train scientists and support research and networking programs in ways that encourage crosstalk and coordination of efforts spanning cellular and molecular neurobiology, toxicology, genetics, epidemiology, and exposure science are needed. Training opportunities should be created around novel statistical and big data approaches geared toward complex data, with the goal of accelerating analyses that address probabilities across multiple variables.

Policy and Ethical Implications of Advances in Genetic and Environmental Science

Increasing the Diversity of Study Participants

New technology and testing can also lead to increases in healthcare disparities, as the newer methods can be expensive and only accessible to those with certain levels of income or people living in certain communities. Researchers and clinicians must be vigilant to avoid this and support policies that enable access to all. Because of differences in population histories, understanding of genetic probabilities in one population may not be informative in others. Thus, more effort must be made to include diverse populations in studies, including genetic studies. As more genetic information becomes available and demand grows for consumer access to this information, there will be a need for more trained professionals who can accurately interpret genetic test results for patients.

Communication and Dissemination of Research Findings

The incredible complexity of interactions among multiple genetic and environmental factors, presents challenges for communicating findings to affected families and the broader public. Many of the factors identified thus far have a modest effect on the likelihood of autism diagnosis or other co-occurring

condition diagnosis, and different combinations of factors likely operate in different autistic individuals. Epidemiologic studies that report associations of specific exposures with autism at the population level can lead to misleading misinterpretation if extrapolated to individual cases, and a focus on individual risks can mask the importance of exposures whose modification could have substantive impact when measured across the population. Moreover, the limitations inherent to observational studies means that results of a single study require additional independent studies for replication and assessment of generalizability. Conflicting findings among studies are common; these may reflect spurious results or an unappreciated dependency of the association on other factors. Additionally, it is particularly difficult to separate the effects of some exposures from other factors, due to inherent collinearity – for example, distinguishing true medication effects from effects due to the underlying health condition for which medication was required. For these reasons, communicating environmental and genetic findings in ASD requires careful attention to context, including providing information about the strength of any newly reported finding on the scale most appropriate for the audience, the difference between causation and correlation/association, the specific potential limitations of any individual study including the possibility of unmeasured confounding, the degree of contribution to autism diagnoses on a population level, and the need for additional studies to confirm the association.

Summary

The overarching goal of research on autism contributing factors is to develop strategies to address the issues that impact quality of life. As genetic and environmental factors that contribute to autism phenotypes continue to be identified, it will be critical to establish relationships among them. In particular, understanding the downstream biological consequences of individual or multiple factors will help to develop and enhance interventions that will maximize positive outcomes for individuals on the autism spectrum. In many cases, genetic and environmental factors for autism are shared by other physical and mental health conditions. Careful consideration of research results is needed in order to ensure that subsequent public health efforts will have broad utility for protecting health beyond the implications for autism, without causing or increasing stigma or bias.

Objectives

OBJECTIVE 1: Strengthen understanding of genetic factors, including resilience factors, that influence autism and its co-occurring conditions across the full diversity and heterogeneity of individuals on the autism spectrum.

Examples:

- Understand the relationship between genes related to autism and co-occurring conditions, phenotypes, and clinical outcomes. and clinical outcomes.
- Ensure inclusion of diverse samples in genetic studies.
- Understand the contribution of regulatory and other non-coding genomic regions to likelihood autism and co-occurring conditions through whole genome sequencing studies and other methods.

OBJECTIVE 2: Understand the influence of environmental exposures on the development and progression of autism and its co-occurring conditions, enabling the development of strategies to maximize positive outcomes.

Examples:

- Characterize the timing of exposures relative to the cascade of events that unfold during brain development to identify and understand the molecular basis of how environmental exposures impact the development of autism and co-occurring conditions.
- Conduct multiple studies in different populations and settings to reconcile disparate findings and establish robust linkages of environmental exposure to autism likelihood.
- Investigate modifiable factors, such as diet and nutrition, that may confer resilience and/or improve quality of life.

OBJECTIVE 3: Expand knowledge about how multiple environmental and genetic factors interact through specific biological mechanisms to manifest in autism phenotypes.

Examples:

- Develop low-burden exposure measures that can be incorporated in large-scale genetic studies, perhaps leveraging innovations in exposomics, epigenomics, metabolomics, and proteomics.
- Reveal functional biological consequences associated with genetic and environmental factors.
- Understand the role of epigenetics in autism and co-occurring conditions.

References

[1] Willsey HR, Willsey AJ, Wang B, State MW. Genomics, convergent neuroscience and progress in understanding autism spectrum disorder. Nat Rev Neurosci. 2022 Jun;23(6):323-341. [PMID: 35440779]

[2] Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An JY, Peng M, Collins R, Grove J, Klei L, Stevens C, Reichert J, Mulhern MS, Artomov M, Gerges S, Sheppard B, Xu X, Bhaduri A, Norman U, Brand H, Schwartz G, Nguyen R, Guerrero EE, Dias C; Autism Sequencing Consortium; iPSYCH-Broad Consortium, Betancur C, Cook EH, Gallagher L, Gill M, Sutcliffe JS, Thurm A, Zwick ME, Børglum AD, State MW, Cicek AE, Talkowski ME, Cutler DJ, Devlin B, Sanders SJ, Roeder K, Daly MJ, Buxbaum JD. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell. 2020 Feb 6;180(3):568-584.e23. doi: 10.1016/j.cell.2019.12.036. Epub 2020 Jan 23. PMID: 31981491; PMCID: PMC7250485.

[3] Myers SM, Challman TD, Bernier R, Bourgeron T, Chung WK, Constantino JN, Eichler EE, Jacquemont S, Miller DT, Mitchell KJ, Zoghbi HY, Martin CL, Ledbetter DH. Insufficient Evidence for "Autism-Specific" Genes. Am J Hum Genet. 2020 May 7;106(5):587-595. doi: 10.1016/j.ajhg.2020.04.004. Epub 2020 Apr 30. PMID: 32359473; PMCID: PMC7212289.

[4] Buxbaum JD, Cutler DJ, Daly MJ, Devlin B, Roeder K, Sanders SJ; Autism Sequencing Consortium. Not All Autism Genes Are Created Equal: A Response to Myers et al. Am J Hum Genet. 2020 Nov 5;107(5):1000-1003. doi: 10.1016/j.ajhg.2020.09.013. PMID: 33157004; PMCID: PMC7675033.

[5] Myers SM, Challman TD, Martin CL, Ledbetter DH. Response to Buxbaum et al. Am J Hum Genet. 2020 Nov 5;107(5):1004. doi: 10.1016/j.ajhg.2020.09.012. PMID: 33157005; PMCID: PMC7674994.

[6] Mahjani B, De Rubeis S, Gustavsson Mahjani C, Mulhern M, Xu X, Klei L, Satterstrom FK, Fu J, Talkowski ME, Reichenberg A, Sandin S, Hultman CM, Grice DE, Roeder K, Devlin B, Buxbaum JD. Prevalence and phenotypic impact of rare potentially damaging variants in autism spectrum disorder. Mol Autism. 2021 Oct 6;12(1):65. doi: 10.1186/s13229-021-00465-3. PMID: 34615535; PMCID: PMC8495954.

[7] Hyman SE. Wringing Biological Insight From Polygenic Signals. Biol Psychiatry. 2021 Jan 1;89(1):8-10. doi: 10.1016/j.biopsych.2020.08.013. PMID: 33272363.

[8] Gandal MJ, Geschwind DH. Polygenicity in Psychiatry-Like It or Not, We Have to Understand It. Biol Psychiatry. 2021 Jan 1;89(1):2-4. doi: 10.1016/j.biopsych.2020.10.002. PMID: 33272361.

[9] Pugsley K, Scherer SW, Bellgrove MA, Hawi Z. Environmental exposures associated with elevated risk for autism spectrum disorder may augment the burden of deleterious de novo mutations among probands. Mol Psychiatry. 2022 Jan;27(1):710-730. doi: 10.1038/s41380-021-01142-w. Epub 2021 May 17. PMID: 34002022; PMCID: PMC8960415.

[10] Constantino JN, Todorov A, Hilton C, Law P, Zhang Y, Molloy E, Fitzgerald R, Geschwind D. Autism recurrence in half siblings: strong support for genetic mechanisms of transmission in ASD. *Mol Psychiatry*. 2013 Feb;18(2):137-8. [PMID: 22371046]

[11] Risch N, Hoffmann TJ, Anderson M, Croen LA, Grether JK, Windham GC. Familial recurrence of autism spectrum disorder: evaluating genetic and environmental contributions. *Am J Psychiatry*. 2014 Nov 1;171(11):1206-13. [PMID: 24969362]

[12] Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. *JAMA*. 2014 May 7;311(17):1770-7. [PMID: 24794370]

[13] Tick B, Bolton P, Happé F, Rutter M, Rijsdijk F. Heritability of autism spectrum disorders: a meta-analysis of twin studies. J Child Psychol Psychiatry. 2016 May;57(5):585-95. doi: 10.1111/jcpp.12499. Epub 2015 Dec 27. PMID: 26709141; PMCID: PMC4996332.

[14] Castelbaum L, Sylvester CM, Zhang Y, Yu Q, Constantino JN. On the Nature of Monozygotic Twin Concordance and Discordance for Autistic Trait Severity: A Quantitative Analysis. Behav Genet. 2020 Jul;50(4):263-272. doi: 10.1007/s10519-019-09987-2. Epub 2019 Dec 18. PMID: 31853901; PMCID: PMC7355281.

[15] Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR; ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium 3, Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015 Nov;47(11):1236-41. [PMID: 26414676]

[16] Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu; Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell. 2019 Dec 12;179(7):1469-1482.e11. doi: 10.1016/j.cell.2019.11.020. PMID: 31835028; PMCID: PMC7077032.

[17] Autism Spectrum Disorders Working Group of The Psychiatric Genomics Consortium. Meta-analysis of GWAS of over 16,000 individuals with autism spectrum disorder highlights a novel locus at 10q24.32 and a significant overlap with schizophrenia. *Mol Autism*. 2017 May 22;8:21. [PMID: 28540026]

[18] Jokiranta-Olkoniemi E, Cheslack-Postava K, Sucksdorff D, Suominen A, Gyllenberg D, Chudal R, Leivonen S, Gissler M, Brown AS, Sourander A. Risk of psychiatric and neurodevelopmental disorders among siblings of probands with autism spectrum disorders. *JAMA Psychiatry*. 2016 Jun 1;73(6):622-9. [PMID: 27145529]

[19] Gillberg C. Chromosomal disorders and autism. *J Autism Dev Disord*. 1998 Oct;28(5):415-25. [PMID: 9813777]

[20] Kielinen M, Rantala H, Timonen E, Linna SL, Moilanen I. Associated medical disorders and disabilities in children with autistic disorder: a population-based study. *Autism*. 2004 Mar;8(1):49-60. [PMID: 15070547]

[21] Fine SE, Weissman A, Gerdes M, Pinto-Martin J, Zackai EH, McDonald-McGinn DM, Emanuel BS. Autism spectrum disorders and symptoms in children with molecularly confirmed 22q11.2 deletion syndrome. *J Autism Dev Disord*. 2005 Aug;35(4):461-70. [PMID: 16134031]

[22] Gillberg IC, Gillberg C, Ahlsén G. Autistic behaviour and attention deficits in tuberous sclerosis: a population-based study. *Dev Med Child Neurol*. 1994 Jan;36(1):50-6. [PMID: 8132114]

[23] Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, Pallesen J, Agerbo E, Andreassen OA, Anney R, Awashti S, Belliveau R, Bettella F, Buxbaum JD, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Christensen JH, Churchhouse C, Dellenvall K, Demontis D, De Rubeis S, Devlin B, Djurovic S, Dumont AL, Goldstein JI, Hansen CS, Hauberg ME, Hollegaard MV, Hope S, Howrigan DP, Huang H, Hultman CM, Klei L, Maller J, Martin J, Martin AR, Moran JL, Nyegaard M, Nærland T, Palmer DS, Palotie A, Pedersen CB, Pedersen MG, dPoterba T, Poulsen JB, Pourcain BS, Qvist P, Rehnström K, Reichenberg A, Reichert J, Robinson EB, Roeder K, Roussos P, Saemundsen E, Sandin S, Satterstrom FK, Davey Smith G, Stefansson H, Steinberg S, Stevens CR, Sullivan PF, Turley P, Walters GB, Xu X; Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium; BUPGEN; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium; 23andMe Research Team, Stefansson K, Geschwind DH, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Neale BM, Daly MJ, Børglum AD. Identification of common genetic risk variants for autism spectrum disorder. Nat Genet. 2019 Mar;51(3):431-444. doi: 10.1038/s41588-019-0344-8. Epub 2019 Feb 25. PMID: 30804558; PMCID: PMC6454898.

[24] Maenner MJ, Shaw KA, Baio J; EdS1, Washington A, Patrick M, DiRienzo M, Christensen DL, Wiggins LD, Pettygrove S, Andrews JG, Lopez M, Hudson A, Baroud T, Schwenk Y, White T, Rosenberg CR, Lee LC, Harrington RA, Huston M, Hewitt A; PhD-7, Esler A, Hall-Lande J, Poynter JN, Hallas-Muchow L, Constantino JN, Fitzgerald RT, Zahorodny W, Shenouda J, Daniels JL, Warren Z, Vehorn A, Salinas A, Durkin MS, Dietz PM. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. MMWR Surveill Summ. 2020 Mar 27;69(4):1-12. doi: 10.15585/mmwr.ss6904a1. Erratum in: MMWR Morb Mortal Wkly Rep. 2020 Apr 24;69(16):503. PMID: 32214087; PMCID: PMC7119644.

[25] Loomes R, Hull L, Mandy WPL. What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry. 2017 Jun;56(6):466-474. doi: 10.1016/j.jaac.2017.03.013. Epub 2017 Apr 5. PMID: 28545751.

[26] Palmer N, Beam A, Agniel D, Eran A, Manrai A, Spettell C, Steinberg G, Mandl K, Fox K, Nelson SF, Kohane I. Association of Sex With Recurrence of Autism Spectrum Disorder Among Siblings. JAMA Pediatr. 2017 Nov 1;171(11):1107-1112. doi: 10.1001/jamapediatrics.2017.2832. PMID: 28973142; PMCID: PMC5710368.

[27] Wigdor EM, Weiner DJ, Grove J, Fu JM, Thompson WK, Carey CE, Baya N, van der Merwe C, Walters RK, Satterstrom FK, Palmer DS, Rosengren A, Bybjerg-Grauholm J, Hougaard DM, Mortensen PB, Daly MJ, Talkowski ME, Sanders SJ, Bishop SL, Børglum AD, Robinson EB. The female protective effect against autism spectrum disorder. *Cell Genomics.* 2022 Jun 8;2(6):100134. https://doi.org/10.1016/j.xgen.2022.100134

[28] Gockley J, Willsey AJ, Dong S, Dougherty JD, Constantino JN, Sanders SJ. The female protective effect in autism spectrum disorder is not mediated by a single genetic locus. Mol Autism. 2015 May 13;6:25. doi: 10.1186/s13229-015-0014-3. PMID: 25973162; PMCID: PMC4429476.

[29] Bai D, Marrus N, Yip BHK, Reichenberg A, Constantino JN, Sandin S. Inherited Risk for Autism Through Maternal and Paternal Lineage. Biol Psychiatry. 2020 Sep 15;88(6):480-487. doi: 10.1016/j.biopsych.2020.03.013. Epub 2020 Apr 2. PMID: 32430199; PMCID: PMC7483301.

[30] Enriquez KD, Gupta AR, Hoffman EJ. Signaling Pathways and Sex Differential Processes in Autism Spectrum Disorder. Front Psychiatry. 2021 Oct 8;12:716673. doi: 10.3389/fpsyt.2021.716673. PMID: 34690830; PMCID: PMC8531220.

[31] Schieve LA, Tian LH, Drews-Botsch C, Windham GC, Newschaffer C, Daniels JL, Lee LC, Croen LA, Danielle Fallin M. Autism spectrum disorder and birth spacing: Findings from the study to explore early development (SEED). Autism Res. 2018 Jan;11(1):81-94. doi: 10.1002/aur.1887. Epub 2017 Nov 22. PMID: 29164825; PMCID: PMC5773391.

[32] Crump C, Sundquist J, Sundquist K. Preterm or Early Term Birth and Risk of Autism. Pediatrics. 2021 Sep;148(3):e2020032300. doi: 10.1542/peds.2020-032300. Epub 2021 Aug 11. PMID: 34380775.

[33] Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing maternal age is associated with increasing risk for autism: a review and meta-analysis. J. Am. Acad. Child Adolesc. *Psychiatry*. 2012 May; 51(5):477–486.e1. [PMID: 22525954]

[34] Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. *Mol. Psychiatry*. 2011 Dec; 16(12):1203–1212. [PMID: 21116277]

[35] Puleo CM, Schmeidler J, Reichenberg A, Kolevzon A, Soorya LV, Buxbaum JD, Silverman JM. Advancing paternal age and simplex autism. *Autism*. 2012 Jul; 16(4):367–380. [PMID: 22180389]

[36] Reichenberg A, Gross R, Sandin S, Susser ES. Advancing paternal and maternal age are both important for autism risk. *Am. J. Public Health*. 2010 May; 100(5):772–773; author reply 773. [PMID: 20299637]

[37] Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, Park BY, Snyder NW, Schendel D, Volk H, Windham GC, Newschaffer C. The changing epidemiology of autism spectrum disorders. *Annu Rev Public Health*. 2017 Mar 20;38:81-102. [PMID: 28068486]

[38] Wild CP. The exposome: from concept to utility. *Int J Epidemiol*. 2012 Feb;41(1):24-32. [PMID: 22296988]

[39] Rappaport SM. Implications of the exposome for exposure science. *J Expo Sci Environ Epidemiol*. 2011 Jan-Feb;21(1):5-9. [PMID: 21081972]

[40] Price EJ, Vitale CM, Miller GW, David A, Barouki R, Audouze K, Walker DI, Antignac JP, Coumoul X, Bessonneau V, Klánová J. Merging the exposome into an integrated framework for "omics" sciences. iScience. 2022 Feb 24;25(3):103976. doi: 10.1016/j.isci.2022.103976. PMID: 35310334; PMCID: PMC8924626.

[41] Arora M, Reichenberg A, Willfors C, Austin C, Gennings C, Berggren S, Lichtenstein P, Anckarsäter H, Tammimies K, Bölte S. Nat Commun. 2017 Jun 1;8:15493. [PMID: 28569757]

[42] Curtin P, Austin C, Curtin A, Gennings C, Arora M; (for the Emergent Dynamical Systems Group), Tammimies K, Willfors C, Berggren S, Siper P, Rai D, Meyering K, Kolevzon A, Mollon J, David AS, Lewis G, Zammit S, Heilbrun L, Palmer RF, Wright RO, Bölte S, Reichenberg A. Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder. Sci Adv. 2018 May 30;4(5):eaat1293. doi: 10.1126/sciadv.aat1293. PMID: 29854952; PMCID: PMC5976276.

[43] Mehta SQ, Behl S, Day PL, Delgado AM, Larson NB, Stromback LR, Huebner AR, DeGrado TR, Davis JM, Jannetto PJ, Howie F, Pandey MK. Evaluation of Zn, Cu, and Se Levels in the North American Autism Spectrum Disorder Population. Front Mol Neurosci. 2021 Apr 29;14:665686. doi: 10.3389/fnmol.2021.665686. Erratum in: Front Mol Neurosci. 2022 Feb 14;15:831799. PMID: 33994944; PMCID: PMC8116541.

[44] Yu M, Tu P, Dolios G, Dassanayake PS, Volk H, Newschaffer C, Fallin MD, Croen L, Lyall K, Schmidt R, Hertz-Picciotto I, Austin C, Arora M, Petrick LM. Tooth biomarkers to characterize the temporal dynamics of the fetal and early-life exposome. Environ Int. 2021 Dec;157:106849. doi: 10.1016/j.envint.2021.106849. Epub 2021 Sep 2. PMID: 34482270; PMCID: PMC8800489.

[45] Chung MK, Smith MR, Lin Y, Walker DI, Jones D, Patel CJ, Kong SW. Plasma metabolomics of autism spectrum disorder and influence of shared components in proband families. Exposome. 2021 Oct 7;1(1):osab004. doi: 10.1093/exposome/osab004. PMID: 35028569; PMCID: PMC8739333.

[46] Smith AM, Natowicz MR, Braas D, Ludwig MA, Ney DM, Donley ELR, Burrier RE, Amaral DG. A Metabolomics Approach to Screening for Autism Risk in the Children's Autism Metabolome Project. Autism Res. 2020 Aug;13(8):1270-1285. doi: 10.1002/aur.2330. Epub 2020 Jun 18. PMID: 32558271; PMCID: PMC7496373.

[47] Zhang P, Carlsten C, Chaleckis R, Hanhineva K, Huang M, Isobe T, Koistinen VM, Meister I, Papazian S, Sdougkou K, Xie H, Martin JW, Rappaport SM, Tsugawa H, Walker DI, Woodruff TJ, Wright RO, Wheelock CE. Defining the Scope of Exposome Studies and Research Needs from a Multidisciplinary Perspective. Environ Sci Technol Lett. 2021 Oct 12;8(10):839-852. doi: 10.1021/acs.estlett.1c00648. Epub 2021 Sep 7. PMID: 34660833; PMCID: PMC8515788.

[48] Esposito G, Azhari A, Borelli JL. Gene × Environment Interaction in Developmental Disorders: Where Do We Stand and What's Next? Front Psychol. 2018 Oct 26;9:2036. doi: 10.3389/fpsyg.2018.02036. PMID: 30416467; PMCID: PMC6212589.

[49] Taylor MJ, Rosenqvist MA, Larsson H, Gillberg C, D'Onofrio BM, Lichtenstein P, Lundström S. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. JAMA Psychiatry. 2020 Sep 1;77(9):936-943. doi: 10.1001/jamapsychiatry.2020.0680. PMID: 32374377; PMCID: PMC7203675.

[50] Gauderman WJ, Mukherjee B, Aschard H, Hsu L, Lewinger JP, Patel CJ, Witte JS, Amos C, Tai CG, Conti D, Torgerson DG, Lee S, Chatterjee N. Update on the state of the science for analytical methods for gene-environment interactions. *Am J Epidemiol*. 2017 Oct 1;186(7):762-770. [PMID: 28978192]

[51] Webb SJ, Garrison MM, Bernier R, McClintic AM, King BH, Mourad PD. Severity of ASD symptoms and their correlation with the presence of copy number variations and exposure to first trimester ultrasound. *Autism Res*. 2017 Mar;10(3):472-484. [PMID: 27582229]

[52] Kim D, Volk H, Girirajan S, Pendergrass S, Hall MA, Verma SS, Schmidt RJ, Hansen RL, Ghosh D, Ludena-Rodriguez Y, Kim K, Ritchie MD, Hertz-Picciotto I, Selleck SB. The joint effect of air pollution exposure and copy number variation on risk for autism. *Autism Res*. 2017 Apr 27. [PMID: 28448694]

[53] Pugsley K, Scherer SW, Bellgrove MA, Hawi Z. Environmental exposures associated with elevated risk for autism spectrum disorder may augment the burden of deleterious de novo mutations among probands. Mol Psychiatry. 2022 Jan;27(1):710-730. doi: 10.1038/s41380-021-01142-w. Epub 2021 May 17. PMID: 34002022; PMCID: PMC8960415.

[54] Ben-Reuven L, Reiner O. Modeling the autistic cell: iPSCs recapitulate developmental principles of syndromic and nonsyndromic ASD. *Dev Growth Differ*. 2016 Jun;58(5):481-91. [PMID: 27111774]

[55] Hogberg HT, Bressler J, Christian KM, Harris G, Makri G, O'Driscoll C, Pamies D, Smirnova L, Wen Z, Hartung T. Toward a 3D model of human brain development for studying gene/environment interactions. *Stem Cell Res Ther*. 2013;4 Suppl 1:S4. [PMID: 24564953]

[56] Langlie J, Mittal R, Finberg A, Bencie NB, Mittal J, Omidian H, Omidi Y, Eshraghi AA. Unraveling pathological mechanisms in neurological disorders: the impact of cell-based and organoid models. Neural Regen Res. 2022 Oct;17(10):2131-2140. doi: 10.4103/1673-5374.335836. PMID: 35259819; PMCID: PMC9083150.

[57] Pearson BL, Simon JM, McCoy ES, Salazar G, Fragola G, Zylka MJ. Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. *Nat Commun*. 2016 Mar 31;7:11173. [PMID: 27029645]

[58] Carter CJ, Blizard RA. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. *Neurochem Int*. 2016 Oct 27. [PMID: 27984170]

[59] Tseng CJ, McDougle CJ, Hooker JM, Zürcher NR. Epigenetics of Autism Spectrum Disorder: Histone Deacetylases. Biol Psychiatry. 2022 Jun 1;91(11):922-933. doi: 10.1016/j.biopsych.2021.11.021. Epub 2021 Dec 10. PMID: 35120709.

[60] Reichard J, Zimmer-Bensch G. The Epigenome in Neurodevelopmental Disorders. Front Neurosci. 2021 Nov 3;15:776809. doi: 10.3389/fnins.2021.776809. PMID: 34803599; PMCID: PMC8595945.

[61] Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, Won H, van Bakel H, Varghese M, Wang Y, Shieh AW, Haney J, Parhami S, Belmont J, Kim M, Moran Losada P, Khan Z, Mleczko J, Xia Y, Dai R, Wang D, Yang YT, Xu M, Fish K, Hof PR, Warrell J, Fitzgerald D, White K, Jaffe AE; PsychENCODE Consortium, Peters MA, Gerstein M, Liu C, Iakoucheva LM, Pinto D, Geschwind DH. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science. 2018 Dec 14;362(6420):eaat8127. doi: 10.1126/science.aat8127. PMID: 30545856; PMCID: PMC6443102.

[62] Hou L, Zhang X, Wang D, Baccarelli A. Environmental chemical exposures and human epigenetics. *Int J Epidemiol*. 2012 Feb;41(1):79-105. [PMID: 22253299]

[63] Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications. *Nat Rev Genet*. 2012 Jan 4;13(2):97-109. [PMID: 22215131]

[64] Bakulski KM, Fallin MD. Epigenetic epidemiology: promises for public health research. *Environ Mol Mutagen*. 2014 Apr;55(3):171-83. [PMID: 24449392]

[65] Meltzer A, Van de Water J. The role of the immune system in autism spectrum disorder. *Neuropsychopharmacology*. 2017 Jan;42(1): 284-298. [PMID: 27534269]

[66] Krakowiak P, Goines PE, Tancredi DJ, Ashwood P, Hansen RL, Hertz-Picciotto I, Van de Water J. Neonatal cytokine profiles associated with autism spectrum disorder. *Biol Psychiatry*. 2017 Mar 1;81(5):442-451. [PMID: 26392128]

[67] Schug TT, Blawas AM, Gray K, Heindel JJ, Lawler CP. Elucidating the links between endocrine disruptors and neurodevelopment. *Endocrinology*. 2015 Jun;156(6):1941-51. [PMID: 25714811]

[68] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. *Nat Neurosci*. 2017 Feb;20(2): 145-155. [PMID: 28092661]

[69] Vuong HE, Hsiao EY. Emerging roles for the gut microbiome in autism spectrum disorder. *Biol Psychiatry*. 2017 Mar 1;81(5):411-423. [PMID: 27773355]

[70] Agirman G, Yu KB, Hsiao EY. Signaling inflammation across the gut-brain axis. Science. 2021 Nov 26;374(6571):1087-1092. doi: 10.1126/science.abi6087. Epub 2021 Nov 25. PMID: 34822299.

[71] Gao B, Chi L, Mahbub R, Bian X, Tu P, Ru H, Lu K. Multi-omics reveals that lead exposure disturbs gut microbiome development, key metabolites, and metabolic pathways. *Chem Res Toxicol*. 2017 Apr 17;30(4):996-1005. [PMID: 28234468]

[72] Lu K, Abo RP, Schlieper KA, Graffam ME, Levine S, Wishnok JS, Swenberg JA, Tannenbaum SR, Fox JG. Arsenic exposure perturbs the gut microbiome and its metabolic profile in mice: an integrated metagenomics and metabolomics analysis. *Environ Health Perspect*. 2014 Mar;122(3):284-91. [PMID: 24413286]

[73] Alava P, Du Laing G, Tack F, De Ryck T, Van De Wiele T. Westernized diets lower arsenic gastrointestinal bioaccessibility but increase microbial arsenic speciation changes in the colon. *Chemosphere*. 2015 Jan;119:757-62. [PMID: 25192650]

[74] dC Rubin SS, Alava P, Zekker I, Du Laing G, Van de Wiele T. Arsenic thiolation and the role of sulfate-reducing bacteria from the human intestinal tract. *Environ Health Perspect*. 2014 Aug;122(8): 817-22. [PMID: 24833621]

[75] Gee GC, Payne-Sturges DC. Environmental health disparities: a framework integrating psychosocial and environmental concepts. *Environ Health Perspect*. 2004 Dec;112(17):1645-53. [PMID: 15579407]

[76] Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23:303-31. [PMID: 11910065]

[77] Adamkiewicz G, Zota AR, Fabian MP, Chahine T, Julien R, Spengler JD, Levy JI. Moving environmental justice indoors: understanding structural influences on residential exposure patterns in low-income communities. *Am J Public Health*. 2011 Dec;101 Suppl 1:S238-45. [PMID: 21836112]

[78] Satterstrom FK, Kosmicki JA, Wang J, Breen MS, De Rubeis S, An JY, Peng M, Collins R, Grove J, Klei L, Stevens C, Reichert J, Mulhern MS, Artomov M, Gerges S, Sheppard B, Xu X, Bhaduri A, Norman U, Brand H, Schwartz G, Nguyen R, Guerrero EE, Dias C; Autism Sequencing Consortium; iPSYCH-Broad Consortium, Betancur C, Cook EH, Gallagher L, Gill M, Sutcliffe JS, Thurm A, Zwick ME, Børglum AD, State MW, Cicek AE, Talkowski ME, Cutler DJ, Devlin B, Sanders SJ, Roeder K, Daly MJ, Buxbaum JD. Large-Scale Exome Sequencing Study Implicates Both Developmental and Functional Changes in the Neurobiology of Autism. Cell. 2020 Feb 6;180(3):568-584.e23. doi: 10.1016/j.cell.2019.12.036. Epub 2020 Jan 23. PMID: 31981491; PMCID: PMC7250485.

[79] Grove J, Ripke S, Als TD, Mattheisen M, Walters RK, Won H, Pallesen J, Agerbo E, Andreassen OA, Anney R, Awashti S, Belliveau R, Bettella F, Buxbaum JD, Bybjerg-Grauholm J, Bækvad-Hansen M, Cerrato F, Chambert K, Christensen JH, Churchhouse C, Dellenvall K, Demontis D, De Rubeis S, Devlin B, Djurovic S, Dumont AL, Goldstein JI, Hansen CS, Hauberg ME, Hollegaard MV, Hope S, Howrigan DP, Huang H, Hultman CM, Klei L, Maller J, Martin J, Martin AR, Moran JL, Nyegaard M, Nærland T, Palmer DS, Palotie A, Pedersen CB, Pedersen MG, dPoterba T, Poulsen JB, Pourcain BS, Qvist P, Rehnström K, Reichenberg A, Reichert J, Robinson EB, Roeder K, Roussos P, Saemundsen E, Sandin S, Satterstrom FK, Davey Smith G, Stefansson H, Steinberg S, Stevens CR, Sullivan PF, Turley P, Walters GB, Xu X; Autism Spectrum Disorder Working Group of the Psychiatric Genomics Consortium; BUPGEN; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium; 23andMe Research Team, Stefansson K, Geschwind DH, Nordentoft M, Hougaard DM, Werge T, Mors O, Mortensen PB, Neale BM, Daly MJ, Børglum AD. Identification of common genetic risk variants for autism spectrum disorder. Nat Genet. 2019 Mar;51(3):431-444. doi: 10.1038/s41588-019-0344-8. Epub 2019 Feb 25. PMID: 30804558; PMCID: PMC6454898.