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. Modifications in more than 100 genes are now known to increase the probability of an autism diagnosis. 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, implicated in additional genetic, psychiatric, or neurodevelopmental conditions. 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. 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. 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. Siblings of children with autism are 10-20 times more likely to receive an autism diagnosis themselves than non-siblings. Several studies of autism in twins have sought to estimate the relative influence of genes and the environment in autism. 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.

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\textsuperscript{15,16}. Autism shares common genetic variations with neuropsychiatric conditions such as schizophrenia\textsuperscript{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\textsuperscript{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\textsuperscript{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 is 4.3 times more prevalent in males vs. females\textsuperscript{24}; other estimates have consistently estimated that males are 3-4 times more likely to be diagnosed with autism than females\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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. 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. 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. 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.
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 in order to understand how these multiple factors may influence each other and in turn influence neurodevelopment. 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. 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.

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. 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. These provide a unique opportunity to assess susceptibility of early developmental processes to environmental influences in the context of defined genetic risk. 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. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 exposures75,76,77. 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 analysis78. 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 subtypes79.
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 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.
- 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


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