Chapter 3: Genetic and Environmental Factors

What Are the Genetic and Environmental Factors that Contribute to Autism and its Co-Occurring Conditions?

Aspirational Goal: Discover genetic and environmental factors that influence the development of autism and its co-occurring conditions in order to better inform diagnosis and interventions to improve outcomes for people on the autism spectrum.

Introduction

Over the past decade, there have been substantial advances in the understanding of factors that contribute to the development of autism and an increased appreciation of the incredible complexity and interplay of genetic and environmental[*] factors in the process. Research in the general population on a variety of chronic conditions has highlighted the fact that environmental factors can affect different people in markedly different ways depending on the individual's genetic background. Therefore, there has been significant interest in better understanding how genes and environmental factors may interact in autism ("gene by environment" interactions). This chapter emphasizes the desire to understand the genetic and environmental factors that influence the characteristics and trajectory of autism across the full breadth of the spectrum. This goes beyond the core characteristics of autism to include co-occurring physical and mental health conditions that can cause varying levels of challenges. There is a critical need to understand the causes of these co-occurring conditions and identify interventions that can improve outcomes.

The neurodiversity movement has influenced the autism community as a whole in recent years as well as the perceptions around autism genetics and environmental research specifically . Prevention of autism was a focus of scientific research in the 1990s and early 2000s, in line with the prevailing notion of at the time that prevention of all disabilities was a goal in medicine. In more recent years, however, this idea has come into question, as appreciation of disabilities as a part of human diversity and a focus on disability rights have become more prominent, and there have been calls for the medical field to eliminate language that might stigmatize or devalue individuals with disabilities. Neurodiversity advocates have similarly voiced concerns about the goals of research to understand the causes of autism, with worries that such research could ultimately lead to eugenics or otherwise stigmatize, devalue, or harm autistic people. The neurodiversity movement has fostered a new appreciation of the role and value of autistic and other neurodiverse people as an integral part of humanity 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 maximizing positive outcomes. Positive outcomes might be reached by identifying biomarkers that will improve screening and diagnosis to link individuals to services more efficiently and effectively. Understanding of contributing factors may also be helpful in developing personalized interventions to meet individual needs. This line of research can also provide more basic

[*] The IACC has adopted a broad definition of studies on "environment" as encompassing research on all non-heritable influences.

information on human development that will improve understanding of autism and other developmental disabilities. Overall, research on factors that contribute to autism and co-occurring conditions continues with a shifted focus toward understanding autism and how positive outcomes for autistic individuals can be maximized.

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 genetics 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 contribute to the core features of autism to varying degrees and, in many cases, are implicated in other 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. In 27% of individuals on the autism spectrum, gene variants that result in disrupted proteins are contributing factors and are associated with co-occurring conditions, including intellectual disability, learning disabilities, and epilepsy[6]. While some ASD diagnoses can be linked to a mutation in a single gene (syndromic autism), more often differences in multiple genes in the same individual (polygenic variation) contribute to the development of autism[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 factors to more accurately identify autism on an individual level.

Autism is highly heritable, with up to 60-90% of autism cases linked to known or unknown genetic factors[9]. Siblings of children with autism are 10-20 times more likely to receive an ASD diagnosis themselves than non-siblings[10,11,12,13]. Several studies of autism in twins have sought to estimate the relative influence of genes and the environment in autism[14]. Most of these studies have identified substantial contributions of both genetic and environmental factors, although the proportions of the two factors and interpretations of the results have varied substantially across studies. 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[15].

In some cases, specific genetic mutations have been linked with particular phenotypes, or outward characteristics. Using this knowledge to identify 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, there is still much to learn about the regulatory and other noncoding (non-gene) regions of the genome to the likelihood of developing autism. These regions of DNA that do not provide the code for a gene are sometimes areas that regulate how or when nearby genes are active, or they serve as signals for other activities within cells. Noncoding DNA regions may play roles in autism that have yet to be discovered.

Genetic Overlap with Co-Occurring Conditions

Autism often co-occurs with other physical health conditions, including sleep disturbances, gastrointestinal issues, and epilepsy (see Chapter 2 for more details). Emerging research is beginning to identify genetic factors that may contribute to these conditions in autistic individuals. For example, researchers used large genetic databases to identify genetic variants in sleep regulation genes that are more prevalent in autistic individuals[16]. Epilepsy and traits of autism are also common in several neurodevelopmental disorders, such as Fragile X syndrome, Rett syndrome, tuberous sclerosis, and Phelan McDermid syndrome[17,18,19,20]. Several mental health conditions also co-occur frequently with autism. Neuropsychiatric and developmental conditions share many genetic factors[21], and different combinations of genetic variants 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[22]. In the future, it will be important to further explore genetic commonalities between autism and co-occurring conditions in order to identify targets for interventions that will improve outcomes.

Environmental Factors

In addition to genetics studies, research on potential environmental factors (i.e. all non-heritable factors) reflect the current understanding that multiple types of factors can influence autism and its co-occurring conditions. This includes studies of environmental exposures such as pesticides[23], hormone disrupting and other industrial chemicals[24], air pollution[25,26], heavy metals[27], as well as other factors, such as parental age[28,29,30], maternal medications and diet[31,32], prenatal infection[33], preterm birth or birth complications[34], and time between pregnancies[35]. Some of these "environmental" factors might themselves be genetically influenced, while others might be mediating the effects of environmental exposures.

While the number of studies investigating the epidemiology of autism is increasing, most potential environmental factors have not been investigated sufficiently to draw firm conclusions[36]. 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 epidemiological studies using large sample sizes may be needed to detect associations between autism or characteristics of interest with exposure, especially for those exposures that are in low doses or less common. In addition, more research is needed to understand the factors that may mediate (or influence the impact of) these exposures and to identify specific vulnerable periods during prenatal and/or postnatal development that are linked to autism, co-occurring conditions, and/or differences in characteristics and outcomes.

As linkages are revealed between exposures and specific characteristics of autism or its co-occurring conditions, public health strategies should be adjusted to help people avoid exposures that are linked to poor outcomes and increase modifiable factors that confer resilience or maximize positive outcomes. 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.

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 biological measurements using methodologies that are not always pratical. 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[37,38,39]. This scientific approach is called "exposomics." In combination with other "omics" approaches, such as metabolomics (measurement of metabolism byproducts), researchers have been able to identify biomarkers associated with autism by analyzing and comparing hair, teeth, or blood serum of individuals with autism and typically developing controls[27, 40,41,42,43,44]. Similar to genomics, exposomic 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 important to address challenges in capturing and integrating many measures over time.

Gene-Environment Interactions

There is general agreement that both environment and genetics contribute to the development and trajectory of autism and its co-occurring conditions. Recent research studies have sought to identify gene-environment interactions[45] in order to understand how these multiple factors may influence each other and in turn influence neurodevelopment[46]. 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 autism 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 is a high priority.

Increasing knowledge of genetics has led scientists to investigate gene pathways that affect neural circuits; it is unlikely that single genes act in isolation to contribute to autistic traits. 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[9]. 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. Studies using model systems, such as human induced pluripotent stem cells (hiPSCs) and brain organoids generated from autistic individuals with a known genetic background, are also being used increasingly to study genetic and environmental contributors to autism[47,48,49]. Approaches that incorporate chemical screening and computational methods in these model systems to identify possible environmental exposures should also be priorities for future research[50,51].

Epigenetics

Identifying how a person's genes can influence how the body responds to exposures is critical for interpretation of autism-exposure associations. Regulation of gene expression (activity), commonly referred to as epigenetics, is a key component in the response to genetic variation and environmental exposures[52,53]. 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. Those regulatory molecules can be influenced by stimuli from the environment, such as chemicals, hormones, light, and nutrients. Changes in the activity of regulatory molecules in response to the environment provides a way for the environment to influence gene activity. Multiple lines of evidence implicate epigenetic changes in development of autism, and several known genetic syndromes that often result in autism, such as Fragile X and Angelman syndrome, have established epigenetic mechanisms. A recent study has characterized how epigenetics influence patterns of variation in autism and other mental health conditions[54]. Results from rare-variant ASD genetic discoveries point to the remodeling of DNA as a shared pathway in autism 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[55,56,57].

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 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[58]; 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[59]. 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[60]. 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 an additional priority area of inquiry. There is increasing evidence for links between the gut microbiome, brain, and behavioral phenotypes relevant to autism[61,62,63]. 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[64,65], particularly during early life when the microbiome is being colonized. A role for the microbiome in the metabolism of environmental chemicals has also been established[66,67]. This means that variations among individuals in microbiome composition can impact how that individual metabolizes environmental chemicals, potentially contributing to variations in the presentation of autism. Small clinical studies using antibiotics or microbiome transplant (fecal transfer) support a potential role for changes in the gut microbiome in contributing to the autism phenotypes. Continued exploration of microbiome function following environmental exposures should further elucidate their influence on autism.

Resources to Accelerate Research on Genetic and Environmental Factors

Large-Scale Studies of Genetic and Environmental Factors

Studies of the genetic architecture of autism 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 sequenced 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 the National Institutes of Health [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[2]. 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[22].

There are similar large-scale efforts to understand environmental factors that contribute to autism. The Study to Explore Early Development (SEED) is a multi-year multi-site study, funded by the Centers for Disease Control and Prevention (CDC), that seeks to identify early behaviors and other factors related to the trajectory of autism that can impact health and well-being. Initially focused on preschool-aged children, SEED recently expanded to study adolescents as well. Findings from SEED studies have demonstrated the impact of several environmental factors on the likelihood of ASD diagnosis. The Environmental Influences on Children's Health Outcomes (ECHO) initiative of the NIH is combining data from more than 60 cohorts comprising over 100,000 people, including approximately 61,000 children. Although the extent of autism-related measures that are, or will be, included in ECHO has not yet been established, this initiative represents an exceptional opportunity to study autism-related traits in large and diverse populations.

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 is critical for ensuring that the data collected is used for maximum value. Combining data across observational studies can yield increased power and strengthen generalizability, but this will require improved standardization of exposure measures and methodologies. 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 developing the analytic approaches needed to help researchers mine data from large or aggregated data sources.

Interdisciplinary Training and Career Development

The workforce needs related to understanding autism contributing factors align with an increasing recognition that answering complex questions will require team science approaches. Programs and opportunities that train scientists and support research in ways that encourage multi-pronged 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 and Studies of Diverse Populations

New technology and testing can also lead to increases in healthcare disparities, as the newer methods can be expensive initially and only accessible to those with certain levels of income or people living in certain communities. Researchers, clinicians, and service providers must be vigilant to avoid this and support policies that enable equitable access for all. Because of differences in population histories, an 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.

Underrepresented minority communities and low-income communities often face disproportionate exposure to harmful environmental exposures[68,69,70]. Additional attention is needed to ensure that these populations are well represented in research on environmental contributors to autism. Ultimately, it will be critical for disparities in environmental factor exposure to be addressed in order to improve equity.

Studies that examine environmental factors within sex-specific subgroups are especially important. However, given the lower ASD diagnosis rate in girls and women, 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 girls and women 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.

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 autism 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 maximize positive outcomes. 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, including those that commonly co-occur with autism. As investigations of genetic and environmental contributing factors continues, it is critical to engage the autism community in discussions about what types of research will be most beneficial for them. Careful consideration of research questions and results is needed in order to ensure that research can be conducted without causing unintentional harms such as stigma toward, discrimination against, or devaluation of autistic people, and to establish subsequent public health efforts that will have broad utility for increasing health and well-being for all people on the autism spectrum.

Recommendations

RECOMMENDATION 1: Strengthen understanding of genetic factors, including resilience factors, that influence autism and its co-occurring conditions across the full diversity 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 participants in genetic studies.
- Understand the contribution of regulatory and other non-coding genomic regions to the likelihood of autism and co-occurring conditions through whole genome sequencing studies and other methods.

RECOMMENDATION 2: Understand the influence of environmental factors 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 environmental exposures relative to the stages of brain development to identify and understand the molecular basis of their impact on autism and co-occurring conditions.
- Conduct multiple studies in different populations and settings to reconcile disparate findings and establish robust linkages of environmental factors to autism likelihood, including in populations and communities that have been underserved.
- Investigate modifiable factors, such as diet and nutrition, that may confer resilience and/or improve outcomes.

RECOMMENDATION 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.

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