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Genomics and Medicine

Which Came First: the Gene or the Environment Factor?

As of today, 1 in every 150 US children has been diagnosed with autism or an autistically linked disorder (DiCicco-Bloom). Considering these proportions approximately over 500,000 children in the United States are diagnosed, and this data only pertains to childhood diagnosis. Autism became a major U.S. concern in 2001, when a U.S. Senate hearing involving the dramatic spike in diagnosis lead to new in depth and prolific autism research, and while autism research has lead to new genetic research it seems that little is known completely about the causes of the disorder or even a complete understanding of its nature (US Govt). Almost a decade later, a new group stands in front of the United States Senate. Following a 600% increase in the prevalence of the disease, Autism Speaks, North America's biggest autism science foundation, drafted a new collaborative research plan to instead focus on the environmental causes of the disease in question. In August 2010, two years after the research's initial drafting of Environmental Factors Initiative, a grant fund and collaborative research project investing in research focused on the environmental causes of autism, Autism Speaks spoke to the Senate about new research comparing both the genetic and environmental factors that are the potential contributors to autism (Rubenstein).

It seems that after almost a decade a research scientists would have some greater light on the autism mystery, but it seems that research has only lead to greater enigma. A lot of this

confusion is due to autism's nature. Autism unlike the common cold is a disorder that is highly variable within each person diagnosed, and even more so it is further complicated by being a mental disorder. The brain- aside from the vastness of genetics- being one of the most complex concepts within medicine is still highly misunderstood and often times any neurological or psychopathic disorder can only be observed or difficult to pinpoint. However, genetic research has played an important role in some understanding, but it seems with the millions of dollars put into research more results would be displayed. Within the last year, the National Institute of Health or the NIH has devoted 136 million dollars to autism research, and the expected amount of research funding for 2011 shows an increase with a projection of approximately 143 million (NIH). There is a competitive aspect to the research proposals presented, and scientists are taking a divergent path in autism research. Many suggest continuing the genetic approach by still focusing on the heritable factors, and from isolating a chromosome or disorder that could possibly lead to a cure or explain the prevalence of the disorder. Others suggest a more preventative means of resolving the issue and have requested that scientific studies now focus on the environmental factors that cause autism expression. Their questions pertaining to what in the environment leads to the activation of the genes previously questioned. Each group looks to find some similarity, either in genes or social backgrounds to ideally find a possible solution, but given the time and money invested in research the question is, what research will bring the greatest knowledge and hopefully solve this pandemic? As research pursues it appears the goals and knowledge gained becomes narrower, however scientific approach should not disregard ambivalence, but instead it should look at the weaknesses and strengths of combined research studies.

This obscurity not only remains in the nature of Autistic Spectrum disorder, but also within the causation of the disease itself. Originally assumed to be a social construct recent studies have proven the genetic validity of autism, but given the profound number of studies the results have only given some limited insight. Autism Spectrum Disorder, or ASD, is actually the name of three different diseases: autism, Asperger's Syndrome, and pervasive developmental disorder (Freitag). As of today, these disorders are now viewed as a variation of one central disorder and diagnosis into one of the three diseases is based on a patient's displayed characteristics. "ASD are characterized by three core features: impairment in reciprocal social interactions, communicative deficits, and repetitive and restricted patterns of behavior and interests" (Burbach). Genetic variability coupled with the range of ASD, even amongst the identified disorders, generates a great range of variation and speculation.

Autism is considered to be one of the most heritably based neurological disorders, statistically shown to have a heritability of approximately 90%. As of 2007, copy number variations or CNV testing has enforced the genetic background of autism (Burbach). A significant number of patients diagnosed with autism have been shown chromosomal abnormality averaging 3-5%. But even with this information CNV consists of a wide range of both chromosomes and affected loci and it is difficult to pinpoint a particular gene and its sequence responsibility. "However, the identified loci are often large, covering many genes, and are often "private" to an individual or family" (Burbach). Additional studies have taken a reverse route, instead focusing on the problem of the biological pathways to identify a possible gene malfunction. Studies have shown that cerebellum development in autism patients is one of the possible reasons for the characteristics of the disorders and in three independent studies the human gene ENGRAILED2, an autism susceptibility gene that is also related to cerebral

development, has been identified. This type of research has shown some very strong relation to the genetics of autism and function (DiCicco-Bloom).

Prevailing studies continue to show a wide variety of genetic background to autism. Myriads of linkage studies have been performed showing that autism is not caused by one single gene, but instead a complex interaction of gene families. For instance "Linkage has been found in at least two independent studies in regions 2q21–33, 3q25–27, 3p25, 4q32, 6q14–21, 7q22, 7q31–36, 11p12–13, 17q11–21 (Freitag)." But even here variability lead to unrepeated findings, but ultimately a definite linkage has been associated with chromosome 7q22. Other linkage studies similar to the one that tracked ENGRAILED2, have been performed with mixed results. Possibly 10 of the 23 human chromosomes could have some abnormality that relates to autism associated characteristics, in accordance with genetic wide association studies some possible 100 variations in gene could cause the disease. These studies are tentative and often focus on a variable physiology to track to gene. However, the occurrence of a fragile X gene has lead to some suspicion of a sex-linked causation-the gene prevailing in 4 to 1 in males. Autism is definitely an inherited disease, but clearly genetic tests have proven that Mendelian inheritance patterns are not the doctrine which the disorder prevails by (Freitag, Lein).

However, genes are not merely defined by their heritability but also the environmental factors that cause gene expression. And scientists are now putting effort into studying the environmental factors that cause autism. Unfortunately environmental studies can be weak, and according to Martha Herbert, a pediatric neurologist at the Massachusetts General Hospital, "Only in the past few years have funding opportunities started to become available to support these types of inquiries, and it is at least in part for this reason that the relatively small share of

the literature devoted to these questions includes studies of varying quality and often with small sample sizes."

Despite the lack of funding for many of these proposals, especially within the United States, some attempts at finding an environmental cause are being taken. The Autism Birth Cohert project is a unique project in that it is taking both genes and environment into account. The studies principle goals are "The Autism Birth Cohort (ABC) was established to address the natural history of ASD, explore genetic and pre- or perinatal environmental factors in causation, as well as the interplay between genes and environment, and to facilitate discovery of biomarkers with potential to enable early recognition and treatment" (Stoltenberg). The cohort surprisingly is one of few studies to actually attempt at finding a biomarker for autism, which would create a more accurate diagnosis system. The current diagnosis process consists of screening of a three year old child on a comparative basis, and children who are not diagnosed at this time are often overlooked (Stoltenberg).

The ABC is an ongoing joint study project between Columbia University and the Norwegian government that arose from the Norwegian Mother and Child Birth Cohort, a population birth study began in 1999. One of the greatest benefits of a project of this kind is the ability to analyze environmental factors by keeping detailed data through questionnaires and minimizing variability. From the Norwegian birth cohort, children born within the allocated period are followed, as well as their parents. Using this data scientists are able to begin by finding ASD cases through the typical diagnosis method, next analyze genetic material of the children and parents, and monitor the family's sociological history (Stoltenberg). While the study is still in its early phases, in 2002 the study found some preliminary causes in the chemical thermisol, a preservative compound used in vaccines (Fink).

In solving the debate, there needs to be not a complete removal of one type of research but instead joint projects that can effectively analyze both the genetic and environmental results. One study has lead to a new proposed model of the chemicals that seem to be associated with autism occurrence. In the Figure A, both the genetic and environment factors lead to the expression of the autism phenotype. Researchers hypothesize that these chemicals could potentially have effect of the degradation of the gene, and over time a gene becomes more susceptible to a particular chemical. Eventually a generation will appear with an observable negative reaction to this chemical and this could be the possible spawn of autism display. This could also account for the diagnosis spike, as each concurrent generation becomes more susceptible to the toxic chemical.

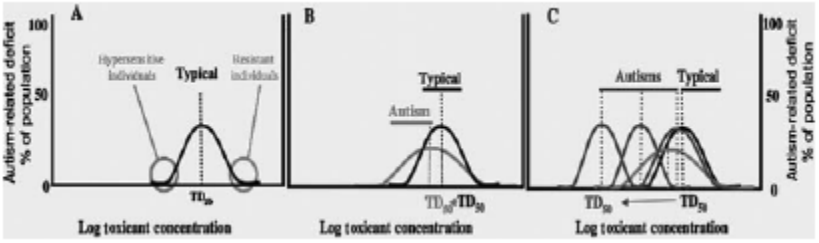

Fig.A. (A) Depiction of how a typically developing population responds to increasing concentrations of a hypothetical environmental toxicant or combination of toxicants. In every population, there are hypersensitive individuals that, due to their genetic makeup, timing of exposure, and/or coincidental illnesses (e.g., viral or bacterial infection), are particularly vulnerable to adverse effects associated with low-level exposures. The TD 50 is the exposure dose of a chemical(s) that produces an autism-related adverse effect in 50% of the population. Resistant individuals are likely to possess more robust metabolic defenses and repair mechanisms. (B) An example of how autism spectrum, grouped as a single population, could influence the mean sensitivity to an environmental exposure. Because of autism's heterogeneity, the distribution about the TD 50 is likely to be broader, thereby adversely affecting a larger fraction of the autism population. (C) Stratification of autism into definable endophenotypes possessing distinct but overlapping sets of susceptibility genes could result in definable subpopulations having different sensitivity to

environmental modifiers of autism-related deficits, severity, and/or treatment outcomes (Image from "What We Need to Know about Gene x Environment Interactions)

Among those susceptible to the xenobiotical chemicals, toxic chemicals that accumulate in an environment, there is a gradient and range of susceptibility. Researches along these fields have been able to find a possible endophenotype biomarker, or a biological indicator that can identify a specific diagnosis amongst the autism spectrum (Lein).

As autism grows in research and diagnosis, so will the conflicts of the means to cure it, but within each argument for resolution is derived some dependence on the opposing view. Research should not merely categorize itself into environment or genetic, but converge these ideas to form a means to resolve this worldwide issue. Even within the human phenotype, both genetics and environment work in concordance and the same should apply for research studies. As of 2007, the National Autism Alliance and Autism speaks have merged to create the biggest privately owned autism research organization, and on November 30th the National Institute of Mental Health announced its first data release. This has remarkable chances for autism research as now researchers can use data from over 10,000 individuals involved in autistic spectrum disorder studies (NIMH). Perhaps, these new mergers and openness establish a new outlook on how research methods should be done, migrating towards an effective complementary system.

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