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# THE SHIFTING ROLE OF GENES IN THE AUTISM EPIDEMIC

BY MARK R. GEIER, MD, PHD, FABMG, FACE, DAVID A. GEIER, BA, AND LISA K. SYKES, MDIV

Only occasionally in history do health authorities mistake the cause of an epidemic illness. One clear example is Minamata Disease, a disease that swept a Japanese fishing village located on Minamata Bay.<sup>1</sup> In the 1950s, the Chisso Company, located near Minamata, dumped waste containing high levels of mercury into the bay. As the inhabitants of the village ate the contaminated fish, many died and many more were disabled. In some cases, whole families died of “Minamata Disease,” and among survivors, children born to mothers with the disease were malformed or afflicted with symptoms such as hand-flapping, gait problems, and speech disorders. Authorities identified the epidemic as “infectious” in nature because, to those who did not know an environmental exposure was taking place, it appeared that the disease was merely spreading from one person to another. Epidemics can occur, however, not only when an infectious agent is spread but also when a significant portion of a population suffers exposure to a toxin as happened in Minamata.

Currently, the United States and other countries face an epidemic of autism spectrum disorders (ASDs). There are numerous papers documenting the massive rise in the US rate of diagnosed ASDs from about 1 child in 2,500 born in the 1980s to more than 1 child in 150 born in the 1990s, with some studies showing a rate exceeding 1 child in 100.<sup>2-5</sup> These studies show that this massive rise cannot be accounted for by changes in diagnostic practices or population migration patterns. It is unreasonable to

assume that individuals diagnosed with an ASD in the 1980s were simply not diagnosed because more than 50% of those diagnosed have few, if any, words and, therefore, must have been identified as having some disabling condition in the 1980s. Those who argue that patients diagnosed with an ASD were simply diagnosed as having mental retardation instead in the 1980s must show that the diagnosis was changed to that of an ASD. Such a supposition would require a massive decline in the rate of diagnosed mental retardation directly proportional to the increased rate of diagnosed ASDs, a phenomenon which is clearly not supported by published studies.

Additionally, those who would deny the very existence of the massive epidemic cannot demonstrate the existence of large number of adults from previous generations diagnosed with an ASD, and the millions of dollars that should currently be dedicated to their care, if they existed. Additionally, common sense and personal experience dictate that the present number of children diagnosed with an ASD simply did not exist in previous generations. How many people - especially educators - recall special education classrooms designated for children with an ASD diagnosis as full and with waiting lists before the 1990s? The reality is that rarely, if ever, did one encounter a child diagnosed with an ASD twenty years ago. Now, not only in the school systems but also in neighborhoods, stores, and parks, one frequently encounters children diagnosed with an ASD. The demand for Medicaid services and spots on Developmental

Disabilities Waivers has never been greater. At the state level of government, the wait for these services can be years long.

Confronted with the ongoing epidemic of ASDs, the national health agencies of the United States are focused on understanding the phenomenon of the ASD epidemic as genetic in origin. For example, the United States National Institutes of Health, National Institute of Mental Health home page asserts that evidence points to genetic factors playing a prominent role in the causes of ASD.<sup>6</sup> Such an argument, however, is untenable because an epidemic is defined as a rapid rise in the rate of a disease. While the rate of an epidemic must increase exponentially, the fastest known genetic changes occur at a rate of only 1% per hundred years. Therefore, to invoke a purely genetic cause for any epidemic is an oxymoron. Not only this fact but also a survey of other analyses demonstrate that genes do not play a *casual* role in ASDs, though we will discuss later how genetic susceptibility does contribute to ASDs.

The first claim among those who insist on arguing that ASDs are purely genetic, is that a significant portion of today's individuals diagnosed with an ASD - often claimed to be 25% or more of the population - have a recognized classical genetic syndrome such as Down syndrome, fragile X syndrome, Rett's syndrome, or Angelman/Prader-Willi syndrome.<sup>7</sup> This claim is simply not true. The data on which this argument is based come from times, such as the 1970s, when the diagnosed rate for ASDs was 1 in 10,000. In this pre-epidemic era, such conditions may well have accounted for a significant portion of children with a non-regressive ASD diagnosis. But as the rate of diagnosed ASDs climbed more than tenfold, with this increase being more substantially among the cases of regressive ASDs, the rate at which these other conditions were co-morbid with the diagnosis of an ASD grew increasingly less, until today it represents a very small percentage of children with an ASD diagnosis. That the percentage of individuals diagnosed with an ASD who also have these other classical genetic disorders has fallen so dramatically, in fact, is actually further proof for the existence of an ASD epidemic.<sup>7</sup> For example, if in the 1970s these classic genetic syndromes accounted for about 25% of all individuals diagnosed with an ASD, and because their rate remained fairly constant while the

population rate of children diagnosed with an ASD increased more than tenfold, they would now account for less than 2.5% of the population of individuals diagnosed with an ASD. This very low rate coincides with current observations made by researchers doing laboratory genetic testing on children diagnosed with an ASD.

Since defenders of "genetic autism" cannot show that classic genetic syndromes account for a significant portion of today's population diagnosed with an ASD, they next claim that ASDs are caused by one or more yet-to-be-discovered genes that directly cause ASDs. Numerous studies, costing millions of dollars, have tried to identify "the gene" or "genes" that are responsible for most cases of ASDs. These studies have had limited or no success in finding such a gene or genes and, in fact, these very studies demonstrate that it is highly unlikely that such a gene or genes will ever be found. A study published in *Nature Genetics* examined only families that had more than one child diagnosed with an ASD, using large chromosome microarray testing to find any statistically significant associations between genetic changes and ASDs.<sup>8</sup> While news reports claimed that the study had found "the autism gene," the study itself found that less than a few percent of subjects examined had an identified weak association with genetic changes. In addition, due to the large number of genes examined, even the weak association was found by the authors themselves not to be statistically significant. Subsequent research has found similar results, except that with expanding resolution in chromosome microarrays (i.e., having more ability to decipher smaller genetic changes), studies now reveal that some of the previously positive genetic associations may have actually been false positives. Finally, in most of the few positive results for genetic changes in individuals diagnosed with an ASD, follow-up testing of the affected subject's parents now show that the changes were present in one of the parents and, therefore, were not *de novo* (meaning "new") but, rather, familial; so, since the parent with the gene clearly did not have an ASD diagnosis, then the gene could not be directly causal for the ASD. With the high resolution of the current chromosome microarrays, it now appears highly unlikely that any such genetic testing will ever find a true genetic cause of ASDs responsible for a significant percentage of those patients who

have the diagnosis, regardless of what size sample is examined.

Any explanation of the cause of ASDs must elucidate why there are far more males affected than females (four or five boys for every girl). Males have been shown to be far more affected than females by ASDs. Hypothetically, for genetics alone to account for the predominance of males over females in the population diagnosed with an ASD, the most likely genetic explanation would be for the causative genes to be recessive on the X chromosome. In such a scenario, since males have only one X chromosome and females have two, males would be far more likely to have an ASD diagnosis than females. For this to be true, the hypothetical autism gene(s) on the X chromosome would have to be inherited exclusively from the mother. This is because, in a male, the gamete (sperm) from the father must supply the Y chromosome, and since males are chromosomally XY, they all get their only X chromosome from their mother's gamete (egg). Therefore, a purely genetic cause of ASDs would be expected to display a maternal inheritance pattern. A maternal inheritance pattern is usually easily identified in a family tree since males are almost exclusively affected and their mothers must be non-affected carriers. Such a pattern is easy to discern in such diseases as hemophilia and Duchene's muscular dystrophy. No such pattern has been reported in families with diagnosed ASDs or in genetic analyses of the X chromosome from patients affected with an ASD diagnosis.

Finally, any discussion of the role of genetics in ASD diagnoses usually begins with concordance studies in identical twins that have grown up separately from one another.<sup>9</sup> This method is used to estimate the genetic causal component of a disorder because identical twins that are raised in different homes are exposed to a different non-genetic milieu. To the extent that the disorder is influenced by non-genetic factors, living in different homes will result in different outcomes with respect to whether or not each twin does or does not develop an ASD. If ASDs were purely genetic, then the identical twins would share exactly the same outcome in regard to their ASD status, regardless of which home they grew up in.

The analysis depends on there being large differences in exposure to non-genetic factors from home to home. Twins studies however, cannot take into account environmental



exposures that are omnipresent. Consider the possible role of vaccines - or some component thereof - in ASDs. Because vaccines are mandated and an immunization schedule is set that covers counties, states, and even the nation, exposure in the case of vaccines is "universal." Regardless of the different locations in which a pair of twins may grow up, they will likely incur the same vaccine exposure. Therefore, obviously there is a strong bias for identical twins to have the same outcome with respect to their developing an ASD whether or not the cause is genetic.

Additional problems in interpreting the outcome of the identical twin analyses with regard to the role of genetics in ASDs include the fact that virtually no studies of these types have been done on US children and that the studies that have been conducted elsewhere were not done during a time when the reported rate of an ASD diagnosis was high. Furthermore, identical twins share the same placenta and amniotic sac and, therefore, their environmental exposures in utero are more similar than non-identical twins or other siblings. Additionally, there is a higher acknowledged risk of damage in utero due to various obstetrical complications that occur more in identical twins than in non-identical twins or other siblings. These additional confounders further bias the results of identical twins studies in determining the role of genetics in ASDs. All of that being said, there are few researchers willing to dispute that genetics does play an important role in ASDs. The overwhelming scientific evidence suggests that genes do not cause ASDs, but rather determine critical susceptibility factor(s) to environmental insults that trigger ASDs.

Widespread and sudden changes in toxic exposures over a wide geographic area rarely happen and, therefore, widespread epidemics due to toxins are also rare. Such exposures can be the result of a natural disaster such as a volcanic eruption or - more

likely - the result of a human mistake. To suggest that the ASD epidemic is the result of a toxic exposure that is global in scope is not outlandish because the source of the exposure is identifiable. National and global vaccination programs have resulted in a toxic exposure that is global in scope because of Thimerosal. Thimerosal is the antiquated preservative, half mercury by weight, used in childhood vaccines.<sup>10</sup> With the addition of new vaccines to the immunization schedule, starting in the early 1990s, the amount of mercury children received was suddenly and massively increased. Since vaccines are distributed globally, two generations of children were injected with this widely recognized but undisclosed neurodevelopmental toxin. The result has been the occurrence of a tragic and avoidable epidemic, which is characterized by a sudden rise in neurodevelopmental disorders among children, and which resulted from the global toxic exposure to Thimerosal from childhood vaccines.<sup>11</sup>

The next question is, if almost all of the children were injected with this greatly increased amount of Thimerosal, why did they not all develop an ASD? The answer is similar to one given in response to this question: "If cigarette smoking causes lung cancer, why doesn't everyone who smokes get lung cancer?" In both cases, the explanation is that only those who are most genetically *susceptible* to damage from these toxins will develop the disorder at lower levels of exposure. In the case of the mercury, multiple studies have demonstrated that those children who cannot easily eliminate mercury are the most likely to be affected. The shifting role of genes in the ASD epidemic, then, is from causality to susceptibility, and in the case of a massive exposure to Thimerosal that has triggered the epidemic, the susceptibility is to mercury.<sup>11</sup>

Mercury is a very unusual and dangerous toxin for several reasons. The first is that, unlike most toxins that are toxic at parts per million, mercury is highly toxic to all organs and tissues *at less than one part per billion*.<sup>12</sup> Mercury is also a very unusual toxin because it is a poison that the body has no ability to detoxify. Most poisons are detoxified by being broken down into simple and less toxic substances, usually in the liver. However, mercury is highly toxic in its elemental form and, therefore, the only way an organism can detoxify mercury is by excretion. Numerous

peer-reviewed studies have demonstrated that children with an ASD diagnosis have a reduced ability to eliminate mercury.<sup>11</sup> For example, studies on first baby haircuts have demonstrated that although children with an ASD diagnosis had more exposure to mercury than neurotypical children, the children diagnosed with an ASD excreted far less mercury in their hair than the neurotypical children.<sup>13</sup> Furthermore, the more severe the ASD diagnosis, the less mercury was found in their hair. This study has now been reproduced by independent investigators.<sup>14</sup> These results indicate that children with an ASD diagnosis have a decreased ability to excrete mercury. By contrast heavy metal levels in baby teeth represent body burden rather than secretion ability. Children with an ASD diagnosis have been shown to have more mercury in their baby teeth than neurotypical children.<sup>15</sup>

The mechanism by which mercury is eliminated from the body has also been widely studied. The major way the body eliminates mercury is through the transsulfuration pathway, which produces glutathione, sulfate, and cysteine.<sup>16</sup> These substances bind to mercury and eliminate it from the body through bile and urine. Numerous studies have shown that children diagnosed with an ASD have reduced levels of glutathione, sulfate, and cysteine, and these reduced levels of glutathione pathway substances are a major reason why susceptible children have a reduced ability to eliminate mercury. Thus, these children are at a higher risk of being damaged by even low levels of mercury, especially mercury in vaccines and other drugs that are administered before, at, and after birth. While not all children exposed to similar levels of mercury in their vaccines develop an ASD, all children with a reduced ability to excrete it are at a higher risk than the general population for developing ASDs.<sup>11,16-18</sup> Extensive genetic analyses of SNPs (single nucleotide polymorphism, pronounced "snip") in genes for enzymes in the glutathione pathway have been done and support the understanding of a genetic susceptibility in subjects diagnosed with an ASD.<sup>19-22</sup>

For example, some of these studies have shown that most subjects diagnosed with an ASD (more than 90%) have at least one SNP in their methylenetetrahydrofolate reductase (MTHFR) gene.<sup>19</sup> The MTHFR gene codes for

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the MTHFR enzyme, an essential enzyme in folate metabolism, which is important in the production of glutathione. Since a SNP in the MTHFR gene makes the MTHFR enzyme work far less efficiently, this contributes to decrease glutathione production,<sup>20</sup> making such an individual more susceptible to suffering mercury intoxication following exposure. This susceptibility to mercury also increases the child's risk of developing an ASD if exposed to mercury. Other genetic studies have confirmed that subjects diagnosed with an ASD had significantly higher rates (about two- to threefold) of SNPs in other genes coding for enzymes (called glutathione transferases or GSTs) that help facilitate the binding of mercury to glutathione than neurotypical subjects.<sup>20-22</sup> These same SNPs were previously shown to result in a decreased capacity to eliminate mercury in mercury exposed human populations.<sup>23</sup> All of these factors increase an individual's genetic susceptibility to mercury and, subsequently, the risk of an individual developing an ASD.

In conclusion, the inconvenient truth about the role of genetics in individuals diagnosed with an ASD is that this role is one of susceptibility - not causality. Overwhelmingly, the genes associated with an ASD diagnosis are those associated with increased susceptibility to mercury toxicity. As in Minamata in the 1950s, so in the vaccinating world from the 1990s to present, a disease epidemic has been caused by a widespread environmental toxic exposure. Tragically, the parallels in these misattributed epidemics include not only that authorities misidentified the disease but also that they failed to identify the toxin - in both cases: mercury. The idea that any significant percentage of diagnosed ASD cases is directly caused by an autism gene(s) has been discredited. For more information about genetic consultations for patients diagnosed with an ASD, please visit [www.asdcenters.com](http://www.asdcenters.com).

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