Introduction. A recently released study hypothesizes that autism may be caused by displacement in sequence of genetic material. The details are rather complicated, and the model apparently requires at least two sequence displacements to work.

This may be a good opportunity to reflect on the genetics of autism. I was inspired to create a model that explains the different ways that genetics may lead to the manifestation of autism. This model can be viewed at http://www.larsperner.com/pdf/autism_genetics.pdf.

Impact of Genetics. Overall, genetics appear to have a strong influence on autism. Studies of concordance among identical twins--or the extent to which both will show autism if one does--have reached different results. One study puts the odds at around 90% while others suggest a rate more like 50%. This question is complicated by two factors--criteria for diagnosis and environmental impacts.

If one uses a strict definition of "autistic disorder," chances that two identical twins will
share this diagnosis are smaller than if more flexible criteria are used. The fact that only one receives a diagnosis does not mean that the other has not inherited characteristics of autism. Studies show that even if an identical twin of a person with autism does not meet the criteria for a diagnosis, he or she is likely to show symptoms that may not reach the threshold for diagnosis. For example, the twin may have Asperger's Syndrome, PDD-NOS, or other characteristics that may fall short of warranting an outright diagnosis.

The shared impact of environment is an additional complicating factor. Ideal studies of identical twins study individuals who have been raised apart, but in autism, it is difficult to find sufficient numbers of people who are both identical twins and raised apart. To some extent, one can control for the environment by comparing observations to “fraternal” (or, to avoid being sexist, “sororal”) twins. However, it is likely that identical twins will have their perceived identities greatly influenced by having a genetically identical other. This may be less important in studying conditions that do not appear to be related to personality, but with the ambiguity and subjective nature of autism, this will be a more significant problem here. It should also be pointed out that identical twins may actually have experienced significant differences in their environment, starting with their respective positions in the womb.

**A One-Gene Model.** First in the model, we see the possibility that one single gene could, in principle, be enough to cause autism. We do not know of such a gene, and several genes could individually result in autism.

**Multiple-Gene Vulnerability Model.** Another model, which Dr. Geraldine Dawson of the University of Washington discussed in her keynote address this summer at the conference of the Autism Society of America, suggests that many genes may be involved in autism.

An individual may need to reach a certain threshold—that is, have at least a critical number of genetic conditions—before any symptoms are shown. Again, it is likely that a large number of genes are involved and that no single one of these genes is necessarily shared by all people on the autistic spectrum. For example, if, say, thirty genes are involved, one may, in the simplest model, need to have any five. It could be that some genes are more important, so that if certain "power genes" are affected, only three might be needed.
“Stressor” Genes in Combination With Autism Genes. Autism often inflicts a great deal of stress on the body. It is possible that certain genes that are not directly associated with autism may, reduce the body’s ability to cope with a smaller number of autism would not have been enough to reach a threshold for the manifestation of autism, reduce the body’s ability to “manage” complications from genes that could, by themselves, have been handled.

Again, for example, if stressor genes are present, it might take only three autism genes—rather than five normally required—for autism to “kick in.” Genetic susceptibility to the accumulation of heavy metals in the blood and intolerance of glutens (typically found among grain based foods) and/or casein (typically found in milk-based foods) are observed frequently in individuals with autism but may not directly cause the condition.

Environmental Vulnerability in Combination With Genes. Another possibility is that the person may suffer from one or more genetic problems that, by themselves, would not lead to autism. However, when combined with autism genes, autism might result.

Problems associated with autism often inflict a great deal of stress on the body, so if another “stressor” gene is present, the body may have fewer resources left to compensate for autism genes that could otherwise have been “managed.” For example, even if genes that result in intolerance to glutens (found in certain kinds of breads) and casein (found in certain milk products) are present, this may leave the body more vulnerable to influence by more “direct” autism genes. Vulnerability to heavy metal accumulation could have a similar impact in combination with autism genes.

In a related situation, environmental complications--such as exposure to toxins, malnutrition, fever, or other illnesses--may stress the body in much the same way as non-autism genes. Again, fewer autism vulnerability genes may be needed to reach the needed threshold.
**Gene Sequence Disruptions.** A special case of a genetic cause of autism is disruptions in gene sequences as discussed in the beginning of this post. Here, the genetic information may be the same as in a non-affected individual, but the sequence of the genetic does may have been corrupted.

This is roughly analogous to information that has been entered into a book or spreadsheet out of order. The effects of genetics appear to be expressed through the creation of proteins that are determined by the genetic code, and a small alteration in sequences may cause considerable reverberations throughout the protein outcome.

"Innocent" But Correlated Genes. One way to "hunt" for autism genes is to study the frequency with which various genes occur among affected individuals relative to rest of the population. Genes that are shared in high numbers are more likely to be implicated. The vastness of the human genome and the large costs of collecting complete data for a large number of people often makes it difficult to use this kind of "brute" force. A shortcut, however, involves a comparison of genetic conditions that have an identifiable physical manifestation. For example, if more people on the autistic spectrum were left handed, we might suspect a common gene. If we know the location of a condition that is observed frequently among people on the autistic spectrum, we can examine the frequencies of such genes in autistic and non-autistic groups. It turns out, however, that the correlation of genetics and traits does not always mean that the same genes are involved in two conditions. Occasionally, it will be reported in the news that a "gene marker" has been found for a particular condition. A gene marker is not a specifically identified gene, but rather a hypothesized gene that is believed to be located within a certain region on a specific gene. The reason why this result comes about has to do with the way that chromosomes are mixed in the reproduction process. Among chromosomes, physical fit between the chromosomes of each parent will be better in some areas than in others. Therefore, genes located near each other are more likely to be inherited together. Here, then, we have an illusory correlation. Autism and certain genetic traits may occur together, but the respective genetic traits do not necessarily cause--or even influence--the expression of autism.

**Genetic Protection.** One additional complication is that there is apparently a certain amount of "backup" material--or "spare" genes--that can be activated if certain genetic material that would otherwise be used is missing. (It can, however, also be a problem if both
the default and the "backup" genes are "turned on.") To the extent that this backup material is consistently available across individuals, irrespective of other genetic differences, this would merely result in a gene being less important in causing autism. However, when this protection "kicks in" less consistently, more "noise" is introduced, obscuring the effects of individual genes.


Conclusion. Autism is a perplexing phenomenon. Individual aspects of the condition are highly confusing by themselves, and many paradoxes have been observed. Genetics--even for relatively simple traits--is also a very challenging field, so it is not surprising that, when the two are considered together, drawing conclusions is difficult. With the mechanics of genetics being somewhat outside by area of knowledge, I cannot offer any credible prediction on how soon--or whether--we breakthroughs in this area may be reached.