What defines us as individuals? Is it our relationships and our interactions with those around us? Is it what we say and how we give voice to our thoughts? Or is it our actions and the subtle complexities of our everyday lives? Clearly, these are all defining characteristics. These characteristics are also the fundamental impairments of autism—communication, social interaction, and mannerism. The latest CSHL research changes the way we think about this disease and human behaviors.

**Spontaneous Mutations**

This spring, a group led by CSHL researchers Jonathan Sebat, Lakshmi Muthuswamy, and Mike Wigler published a landmark finding the causes of autism, revealing spontaneous mutations in the genome—known as copy number variants—as a major cause of the disorder. Spontaneous mutations are duplications or deletions that are not inherited from one’s parents. Rather, they are acquired at inception when certain sequences of genetic code fail to copy properly. When an individual acquires a copy number variation (CNV), he effectively acquires a genome that is, in part, unrelated to that of his parents. The paper found that CNVs are far more common than had previously been suspected. Moreover, it suggests that CNVs may be fundamental determinants of other common but complex genetic disorders.

It has been known for some time that identical twins tend to be between 70 and 90% concordant for autism. This suggests that the disorder is highly genetic in origin. Siblings, however, tend to be concordant for autism at most 10% of the time, suggesting a much lower rate of inheritance. The ambiguity in these findings led the CSHL group to hypothesize that the disorder may be more complex than could be accounted for by traditional research approaches. They proposed that while the disorder was clearly genetic, it may not be entirely heritable.
A New Approach

Wigler pitched this hypothesis to CSHL benefactor Jim Simons, whose own daughter has been diagnosed with the autistic spectrum disorder, Asperger’s syndrome. Support from the Simons Foundation enabled the group to collect genome samples from 264 families—over 1,000 individuals in total. Of these families, 118 were “simplex”, which means one family member (a son or daughter) presented with autism. Forty-seven families were “multiplex”, where multiple siblings are affected, and there were 99 controls. Finding and genotyping these individuals was hugely demanding, and the innovative nature of the study made it all the more challenging. “Before our study, very few researchers had considered the potential impact of spontaneous, uninherited mutations,” recalled Muthuswamy. “Previously, it was thought that the most useful samples were from families where more than one child was affected. If autism were strictly an inherited disorder, this would be true.”

Because the CSHL approach was so novel, the team was forced to invent new tools and new methods of data processing. “It required tremendous cooperation between many people with many different types of abilities that are not typically found in biology. That’s why it’s necessary for CSHL to expand and bring in people who are strong in quantitative sciences such as computer science, mathematics, statistics, and physics,” explained Wigler.

In many ways this approach pushes the boundaries of genomic research, and this approach is reflected in the technology behind the study. Representational Oligonucleotide Microarray Analysis (ROMA) is a technique pioneered by Wigler and CSHL colleague Rob Lucito that essentially allows researchers to take a snapshot of an individual’s entire genome. This is accomplished by cutting the genomic sequence into 200,000 fragments, each of which is attached to a probe on a microarray. Each probe is a detector that can, after mathematical processing, determine how many copies of a gene an individual has. By characterizing entire families, the researchers can compare whether sequences in a child’s genome are identical to his or her parents or whether it contains variants that were not copied correctly. They investigated whether these variants were more common in autistic individuals.

The results were staggering—the simplex group had ten times as many copy number variants—a finding that necessitates a profound shift in what we regard as the basis of the autism. Clearly, it remains very much a genetic disorder, just not necessarily an inherited one. CNVs were found to be causal in 10% of simplex families. According to Wigler this is only the tip of the iceberg. “If our technology were more powerful and we could dissect the genome into 2 million as opposed to 200,000 fragments, a conservative estimate is that we’d see 45 to 50% of cases like this.” This finding has implications beyond autism, changing how we regard the whole field of genetics in terms of disease and in terms of inheritance in general. CNVs are likely to underlie most other polygenic disorders, and the CSHL group has already begun to see similar results in schizophrenia.

You Are Unique

Moreover, smaller variants are likely to exist at an exponentially higher level—each one of us may have one or two minor genomic sequences that are effectively unique to us alone. This poses an unexpected philosophical proposition. “The genome has a much higher level of plasticity than was previously appreciated. This is important when you look at the degree to which we don’t share genes. Your family is totally different from any other family in the world and you really are unique,” explained Sebat.

In all likelihood we are all completely different. Spontaneous mutations are just that—spontaneous, unpredicted, random. It is interesting to ponder, therefore, that not only are you the product of your genes or your environment, but you are also the product of chance. “It is pretty fascinating. It is a window into how our personalities are constructed,” said Wigler.

The researchers are now pursuing a major follow-up investigation. With continued support from the Simons Foundation, the project is expanding to sample between 8,000 to 10,000 individuals. The collection will be the country’s largest simplex collection and will undoubtedly shed further light on the causes of autism. “It is the force that’s going to shift the field,” predicts Sebat. John Connolly