Seeing double (or triple) in genome sequencing

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Identical twins have always been assumed to be exactly that – identical, right down to the genetic level. But a new study by University of Western Ontario molecular geneticist Shiva Singh and his colleagues say this is not exactly the case.

For the past 20 years, the distinguished university professor has been working with Dr. Richard O'Reilly, a psychiatry professor at Western, to determine the genetic sequencing of schizophrenia using monozygotic or identical twins.

"The most informative feature of schizophrenia is that it sometimes runs in the family. So, for example, the risk of developing schizophrenia is much higher if you have your brother, sister or mother, father affected with the disease," Singh says, noting in the general population about one per cent have schizophrenia.

"I have been teaching my students that monozygotic twins are genetically identical," he says. "If schizophrenia is a genetic disease and one of them had schizophrenia, the risk for the other twin is supposed to be 100 per cent."

But Singh's study showed the risk was only about 50 per cent. Although this puts them at higher risk than the general population, this proves that there is more to the story than family pedigree.

It took significant technological advances in genetic sequencing for

Singh's research to become possible.

In 2003, the first human DNA sequence was generated. Since those early days, the cost has dropped dramatically from billions of dollars to thousands, making research in this area more cost-effective. Singh and his team examined about one million genetic markers of identical twins (and their two parents), where only one twin had schizophrenia, for his recently published article, Ontogenetic De Novo Copy Number Variations (CNVs) as a Source of Genetic Individuality: Studies on Two Families with MZD Twins with Schizophrenia.

Since only one of the twins has schizophrenia, researchers hoped to find answers in the genes about what causes schizophrenia to develop in one monozygotic twin and not the other.

"We know it is an inherited disorder and genetics play a major role," O'Reilly says. "It's logical that in some identical twins discordant for schizophrenia (one has it and the other doesn't), one or several of those differences will be the factor that has caused that twin to develop schizophrenia.

"Our role in using twins is to identify genes that are candidates and to cross-reference with other groups, such as using genome-wide association studies."

Schizophrenia affects people in adolescence and early adult life.

"This is the most serious of the major mental illnesses," O'Reilly says. "Identifying a better understanding of what is happening at the brain level, what pathways are involved, I think provide a real opportunity for improved treatments.

"If we had a genetic test for schizophrenia, that could be applied early in

the disease when it is difficult to make that diagnosis."

Genetic concepts identified over 150 years have provided foundations for principles governing familial patterns including disease causations. They assume we receive half of our genes from mother and the matching half from the father. Also, all humans have the same number of genes, one copy of each gene from each parent. Further whatever we receive from our parents determines the sum total of our genetic endowment as it is replicated and passed on to all our cells during growth and development.

Consequently monozygotic twins who develop from a single zygote are expected to be genetically identical. This conceptual genetic understanding has allowed us to use and misuse the science of genetics over the years.

Understanding genetic individuality is the key to personalized medicine, however what causes changes in the gene pool is poorly understood. Identical twins have been used for several decades in genetic studies and seem to be ideal candidates for unraveling the mysteries of genetic diseases, such as schizophrenia.

But Singh discovered there might be more differences between the twins than originally thought.

"By looking at the million DNA differences between these pairs, all of a sudden I realized … these guys have differences. They are not genetically identical. So if they are not genetically identical and schizophrenia is in the genes, then these differences that I look and find must have something to do with the disease."

It is these differences Singh believes add proof to the fact everyone has a unique genetic roadmap.

No two of us are alike, even identical twins.

While he has a better understanding of the DNA differences between identical twins by looking at these markers, Singh wants to complete the picture by identifying the entire genome sequences.

For some, generating complete genome sequencing of a person is like looking into a crystal ball to see the past, present and future. The genetic makeup can offer clues about one's susceptibility to certain diseases or conditions.

This crystal-ball mentality, Singh claims, is all "hype."

"I say it is unrealistic. It is not possible at all. The best you can do is a guess; invariably your guess is going to be wrong," he says, noting there are a few added complicating factors to the human puzzle.

"We say, 'a human genome is a human genome, is a human genome. We are all the same, right?' I say wrong because maybe the sequence is similar, but the copy number (dose) of a number of genes I found in different individuals was different." They do not have one copy from mother and the other from father.

What this means is about 12 per cent of DNA can vary across individuals. Even within a person, different cells may have a different copy number of a gene. Learning this has opened up new horizons beyond unraveling the mysteries of schizophrenia.

"Cells are dividing as we develop and differentiate. More important, these cells may loose or acquire additional DNA," Singh says. "Increasing or decreasing the copy number are the mechanisms by which they acquire different amounts of DNA."

Some genes, such as those in the brain, are notorious for acquiring more or less DNA. And the evolution doesn't stop once a person reaches a certain age.

Imagine during fertilization a fetus receives one copy of a gene from each parent. But, during development, the copy of the mother's genes replicates three times, and the number of the father's genes stay the same. Suddenly, the person has four copies of this DNA.

"It has nothing to do with mom's side or dad's side; it has to do with the function," Singh says. "Your mom and dad gave you something, but it is up to you to build on it by acquiring new mutations or copy number of different stretches of genes carrying different set of genes."

The mechanism that causes genes to increase or decrease in number is not yet known.

Singh says determining a person's genetic roadmap through genome sequencing is only the beginning.

"Knowing sequence is important, but that's not everything in terms of predictions for the future," he says.

The number of changes that occur at the genetic level throughout a person's lifetime makes personalized medicine a complex and far-reaching reality. A targeted therapy might work today but due to genetic changes it might not be effective with aging.

"The genome is not static," he says. "It's not that you got it from your parents and you will pass it along to the next generation, (and) in the meantime, they can determine everything you are going to be."

There are many more factors at work, Singh explains.

Building on what they have already learned, Singh and his fellow researchers are working towards generating complete genome sequences of the twins in his study and analyze this to pinpoint where one twin differs from the other, what is the mechanism and ultimately what are consequences of such acquired differences.

This will allow researchers to determine the genetic determinants of schizophrenia, which can be compared to a databank of other patients living with the disease. This genome-wide approach developed by Singh and his team is novel, first of its type in the world. It also has the potential to be effective where all other approaches have not been effective.

“I am looking forward to finding more answers,” he says. “It’s a tough nut to crack.”

Provided by University of Western Ontario