Photo Courtesy of Vivian Cheung

Vivian Cheung, M.D.

Vivian Cheung received a B.S. in Microbiology from the University of California at Los Angeles and a medical degree from Tufts University School of Medicine. She is the William Wikoff Smith Chair in Pediatric Genomics and the Joseph Stokes Investigator at the Children's Hospital of Philadelphia. Dr. Cheung currently practices at the Children's Hospital of Philadelphia and is an Assistant Professor in the University of Pennsylvania School of Medicine. Her research focuses on the genetics of gene expression and radiosensitivity in humans.

What is your specific field of research?

Our interest is identifying the genetic variation in humans. Obviously, our DNA differs, and our sequences aren't identical. Certainly, the majority of our DNA is the same, but that portion that differs between us, what are the contributions of those genetic variations to phenotypes? Why am I more susceptible to or more sensitive to radiation or to certain drugs than maybe you are? Can we identify the genetic sequences that contribute to sensitivity or whatever?

In the lab right now, on the basic science side, we are studying how those variations are affecting the expression level of genes. Certainly we know the DNA-RNA-protein central dogma, but DNA-RNA-protein expression levels of genes vary a lot. So there might be some genes in your B cells that are expressed tenfold higher than in mine—what regulates that? We are developing ways to find the DNA sequence that allows us to understand what makes the expression level of one gene higher in one person than in another person. Since gene expression really affects how a cell functions, it can help us as at an intermediate step how cells work and how they function. So that's the really basic level of the question we're addressing, regulation of gene expression.

On the more applied side, we're trying to understand how these genetic variants affect sensitivity to therapeutics, for example radiation, which we are very interested in. Radiation is used in about 50% of all cancer therapy, and often in a lot of diagnostic tools: CT scans, X-rays, and so on. About 15% of patients who are exposed to radiation develop some sort of side effect. So we would like to know in advance who is going to develop side effects, so that if someone is more sensitive, we can start them on a lower dose. We'd like to be able to map the genes and the genetic variation that increases or decreases peoples' risk or sensitivity to radiation.

It's particularly hard because there are many things you can do to people or drugs that you can give to people, and you can assess their response. You cannot expose people to radiation. The first large-scale analysis was done by someone from Michigan who was studying the affect of the atomic bomb in Japan. He observed how people around the bomb area responded, which gave some hint that there is some sort of genetic basis, there are some families that tend to be more resistant than others. More recently, the Chernobyl incident also gave some data. There are also some studies, for example with breast cancer patients, who have been treated with radiation. People have noticed that if a family member is sensitive to radiation, it suggests that other families are also more sensitive. These are hints, but certainly there has been no formal analysis.

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Because there is not very much data, how do you study these effects?

We think that human cells will teach us more than animal models. We have cell lines from individuals and from many families. One of our study subjects is 45CEPH, an organization that has collected these families. And these are all three-generation families with somewhere from eight to thirteen children. So we have really large families with cell lines of transformed B cells from every individual. We can expose these cell families and see how they respond to radiation. We look for changes in gene expression, or other cell morphology, or cell survival, cell cycle, to understand how these individuals within families and between families respond to radiation. We use these phenotypes to do classical mapping to see what part of the genome they share within family or between families, which give them similar or dissimilar phenotypes. The Human Genome Project has given us so many tools, we can now follow many sites along the genome, and computational methods have improved. We really can bring together computational methods and modern-day genomics to study pretty complex phenotypes.

With the changes in technology, how has the way you do research changed since you began in the field, and in what ways has it impacted your work?

Having faster and more efficient computational abilities have changed my research greatly. Instead of looking at the effect of one genetic variant at a time, we can now look at a half a million, a million, and many millions. Obviously, cells don't look at one genetic variant at a time, so we can get closer to what the biological reality is with these new tools. The fact that we can measure these genetic variants very efficiently with tools such as microarrays and CHIPs, we can assay up to half a million or a million genetic variants using a minimal processing of DNA. Overnight, we get data on half a million or a million sites on the genome. It makes it

easier for us to ask larger-scale questions and take into account more variables.

Do you find that this wealth of information is overwhelming?

I think our ability to understand what all this information is telling us is still limited, but probably having this information is beneficial. It forces us to develop new analytical methods and to ask questions about how to combine information at either the DNA level or gene expression level, or at multiple levels. I think information is always good. It encourages us and it's also our responsibility to think of ways to analyze them more efficiently.

What would you say was your greatest challenge in doing this research?

It is really trying to think about how to apply what we do in the lab to the patients. I do find the gap is still really wide. A lot of the information we know in the lab oftentimes is still not translated into patient care. Some of it is that the information we know in research is not necessarily 100%. For example, we might know that a genetic variant increases risk to radiation or a drug by twofold. How do you use that piece of information—do you not give the drug to the patient because that patient is more likely to have a negative response? But that drug also carries an advantage to that patient - it might cure that person's disease. So the question of how we weigh that information is still in the very early days. I think that the next challenge to human genetics is that as a community and as researchers we need to think about the meaning of our findings and how it applies to patients and people. We can't just see it as a laboratory report we get to publish.

What do you feel about the role of women in science?

The glass ceiling [for women in science] is very real. When you go to meetings, there are fewer women, but if you look at the undergraduate classes, there are not fewer women. What happens as one moves up? I have been very lucky; my husband is in academia, so I think he understands the demands of academia. The job [in academia] is also not so demanding that it makes things impossible. I'm still pretty active in church, it's an aspect of my life that is important to me. I don't feel like I don't have time to do the non-science things in life. But having a supportive spouse is very helpful.

The world is changing to some extent, but I think that academia and society need to think about their different expectations for men and women. For scientific accomplishment, oftentimes the same goals are required, so how do we meet these and help women to achieve these things? I think that mentoring is everything. There are more women entering the biomedical engineering or computational fields, and they need mentors.

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It's also a question of opportunity and personality. When men are trying to do something, they are aggressive and just do it, but when women are trying to accomplish something, they are seen as aggressive. So how do you balance this? And I think as more and more women become involved, you will see more and more role models and it will become easier for women. There are so many role models out there for men, I think we just need to do that for women.

Do you practice medicine now?

Yes. After my post-doctorate fellowship, I came to Penn for a neurology fellowship, during which I started a lab that has led to my dual life in medicine and research. I'm doing mostly research now, but I do still see some patients. I think it's very important if I want to bring my science into patient care to have that link. Otherwise, I really will lose track of the patients' needs and how to bring what we find in the lab to the patients.

In your opinion, to what extent today do you still need to go to medical school to be involved in medical-related research?

There are amazing things we can do in the lab. But looking at medicine, there are a lot of things that are pretty primitive. A lot of things are based more on experience rather than science. We know that certain antibiotics usually work for maybe a child with an ear infection. But we never think about what is causing the ear infection, what the genetic makeup of the patient is that might make them more sensitive to the drug and cause them to develop strong side effects. These things are usually known on the basic science front, but aren't translated to medicine.

Unless you've gone to medical school and have gone through the process of understanding how medicine is practiced, it's pretty hard to make that transition from the bench to the bedside. There are some things that work well in labs that would be completely impractical for patients, from the bedside point of view. I find that medical school training helped me to think about my science better, and how to bring my science into patient care better.

— Interviewed by Zen Liu