Genomics is Changing Causation Evidence in the Courtroom Forever

An Interview with Gary Marchant, JD, Ph.D.

INNOVATIVE SCIENCE SOLUTIONS, LLC
SCIENTIFIC CONSULTANTS to INDUSTRY and COUNSEL
67 Park Place East • Morristown, NJ 07960 • 973-889-1600
www.innovativescience.net

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Genomic science is finding its way into multiple facets of our legal system and it is establishing itself as a major force changing the face of causation evidence in the courtroom. We recently caught up with Gary Marchant to talk about his view on the role of genomics in the legal arena and his view on how this science is likely to change the practice of law in complex cases involving personal injury, product liability, toxic tort, and intellectual property cases.

Gary Marchant is a professor at Arizona State University (ASU) Sandra Day O'Connor College of Law where he teaches courses related to environmental and health sciences, technology, genetics, and the law. Gary, however, is not your typical law professor. In addition to his JD, Gary has a Ph.D. in genetics and a degree in public policy. With that knowledge in hand, Gary has been, and remains, way out ahead of most lawyers in appreciating the intersection between molecular biology and the legal rules for "toxic tort" litigation.

Gary's research interests include the use of genetic information in environmental regulation, risk and the precautionary principle, legal aspects of personalized medicine, and regulation of emerging technologies such as nanotechnology, neuroscience and biotechnology. With so many interests, Gary joined ASU precisely because the undergraduate and graduate schools are very focused on and believe in multi-disciplinary thinking. Over time, one result was the creation of the law school's Center for Law, Science and Innovation, an institution where Gary and others push forward with conferences, meetings and papers that are breaking new ground on important topics at the intersection of science and the law. The Center also publishes a wide-ranging blog, Bits, Blots, and Biomarkers, that covers new developments related to genetic science and the law.

In 2009, Gary and his colleagues published a groundbreaking article that every toxic tort lawyer should read.

Prior to joining the ASU faculty in 1999, Gary was a partner at the Washington, D.C., office of Kirkland & Ellis, where his practice focused on environmental and administrative law. Gary has spent the last 15 years trying to understand more about the role of genomic and epigenetic technologies in toxic tort cases.

How has your formal scientific training affect your thinking and practice as a private practitioner and your teaching and research as a law professor at ASU?

Very much. I was surprised at how much the two areas intersected and how so much of our current practice and teaching of law today involves technology. When I began law school, I threw away all my science textbooks and ended up having to buy them back again. I like opportunities where I can use my scientific background to practice law, even if they do not involve the exact areas I studied in science, but having some familiarity with the scientific process and in scientific publications sure helps.

My degree in genetics was immensely helpful to me personally, and it also was a great selling card for our firm to attract clients. I felt I had a strong ability to communicate more effectively with scientists and clients. I was able to speak their language, and that was incredibly useful to our practice. So I tell my students now that even if they lack scientific training, they will be better lawyers if they have a strong working knowledge of science, and are comfortable with scientific literature and scientific concepts. Every industry in our society now is involved in technology or science in some way, and it's going to be easier to succeed – and serve clients well – if law students and lawyers invest in learning more about some basic principles and processes.

What exactly is genomic technology, -omics, and epigenetics? Do you think these techniques are going to have an impact in the courtroom?

There are two different types of genomic information that are relevant to the courtroom. One is the genomic information you're born with, including the billions of base pairs that form at the moment of conception. We're now able to find out a lot about which variations affect

how we metabolize things coming in to our body, whether they are drugs, chemicals, or food, which are some of the more variable ones. We can now identify which of those genes we have. We're moving very quickly into the world of whole-genome sequencing. I imagine that in the next five or ten years, most people are going to have their whole genome on a chip, and so it's going to show right there what things you are more susceptible and less susceptible to, what genes you have that make you more likely to get diseases, and whether you will live longer or live shorter. All that is going to be right there. So this black box will now be a known quantity that we can look at in litigation. That's going to have all kinds of profound implications.

The second major type of genomic information is changes that occur to our genome that are brought about by certain exposures or other things we encounter in our life. This involves changes to the gene or changes to the gene expression and which genes get turned on or off. The term epigenetics as used as an umbrella for some of these processes. Cancer treatment has been completely revolutionized in the last two years because they're now looking at the tumor and genetic and epigenetic changes to try to figure out what therapy is best for you.

And these techniques will also have major legal implications for toxic tort litigation. The detailed findings scientists can now produce will help to show if or how you've been injured or that you've been exposed to a chemical or that you can quantify an exposure. In some instances, the analysis may exonerate a defendant. Genomic data also will be used to show that you are at risk of a certain disease because of your past exposure. These types of questions will now actually be testable with actual data. These questions and data will revolutionize personal injury litigation.

Can you clarify the difference between an –omic approach and an epigenetic approach?

They sort of merge. The –omic approach is looking at the actual genes you're born with and then assessing *how* those genes are expressed, *which* genes get expressed, and *which do not* get expressed. Epigenetics is a newer idea; it's about what the actual factors are that change your gene expression. These influences—whether they're chemicals or other exposures—that change which genes get expressed in different parts of your body, either normally are abnormally, is called epigenetics. And there's been a revolution in our understanding of these concepts over the last few years.

One important finding is that the time period in which you are exposed is incredibly critical. A second factor is that, unlike a change to your genetic sequence, an epigenetic change is or may be reversible, which has enormous implications. The really surprising finding is that some of these changes can get transmitted to future generations even though they don't involve changes to the gene sequence. So epigenetics is really becoming a part of –omics because –omics includes which genes are turned on or off as well as which genes you have.

So let's say people have identical genetic sequences – e.g., identical twins. Could epigenetic phenomena have a differential impact on each sibling?

Absolutely. Because of environmental influences, epigenetic factors could determine which genes get turned on or off. The epigenetic changes now merge your genome with your environmental exposures. Studies have shown that identical twins born with exactly the same genes diverge in their genetic expression as they age because of different epigenetic influences.

Give an example of what you believe the scientific evidence in a toxic torts case might look like in twenty years.

So, I think that, in twenty years, almost everyone's going to have his or her whole genome on a chip. Therefore, the defense will look at that data for the plaintiff and interrogate it to look for factors that could be used in defending against a liability. A plaintiff, in contrast, will

be able to look at that same data for factors that might increase the case for liability or causation. So both sides will use this information to go beyond the evidence we have now, which is imprecise and non-individualistic. Both sides will also be able to look at a particular individual for indications of what did or did not cause their outcome or illness or whatever they have. That's going to be the revolution. Genomic information will come into play in almost every case, even accident cases, because how you respond to an accident, what your life expectancy is going to be, is partly determined by this information, which is going to be easily available to both sides.

So I see this becoming a major part of future litigation, but it's going to raise a lot of profound legal doctrinal and policy issues as well as ethical debates.

Some have said that the age of epidemiology in the courtroom will be over in the next decade. What does that mean to you in the context of using genetic information to help us in these cases?

I agree with that because I think there's always been a tremendous mismatch between epidemiological data and studies and personal injury litigation. In the litigation arena, you're always looking at an individual—what caused this particular effect in this particular individual. An epidemiologist can't answer that; he can only give probabilities, and those probabilities are always over-inclusive or under-inclusive.

What we can now do with molecular and genetic information is to look at a particular individual. It's not so much: "Can this chemical cause this effect in this group of people?" You can now go in and bear down on a specific individual or group of individuals and say: "Did it cause the effect in this individual?" By looking at molecular and genetic changes, you can ask: "Did this chemical cause a change in person A but not in person B?"

And that's a revolutionary change that will really move us beyond this incredible injustice we currently have in our legal system, where we sometimes over-compensate and other times under-compensate.

Would it be fair to say that genomics is really a tool for specific causation as opposed to general causation?

Yes. But once you can show specific causation, you are, by definition, showing general causation. We never really had any tool that turned it around like that. Using genomics, we start with the individual and go toward the population.

What kind of toxic tort cases will lend themselves most to genomic techniques?

I think the biggest type of case that will benefit from genomic techniques is the one where people have a fairly common disease outcome that could be caused by a lot of different things. Right now we're incapable of teasing out which lung cancers or brain tumors or leukemias are caused by a particular agent or exposure. Using genomic techniques, we'll be able to tease these things apart for many people, and that's going to be revolutionary.

Right now, we're operating in this great cloud of uncertainty and don't have any precision at all. This probably means that more cases will be brought because, right now, if you have lung cancer, unless you are a smoker, you have no idea of what may have been the cause. But with genomics, we may be able to figure that out.

The other thing, which I think is more disconcerting and problematic for the legal system in the long term, is that we all get exposed to things and we don't bring law suits because there is no data to show that the plaintiff may be at risk. However, now, if we start collecting actual latent risk data on each of us, which is quantified, objective, and empirical and that shows molecular changes in our blood, in our genes, how is our legal system going to deal with that? Are we all going to become plaintiffs? Maybe that'll solve the economic woes.

The changes ahead could flood our litigation system unless we create some rules and a threshold that people have to meet to avoid an unrealistic burden on our legal system. Otherwise, you're going to have huge medical monitoring classes for basically every product on sale in this country. The legal system faces challenges to adapt because science moves very quickly these days, and

because so many substances ("natural" or not) create the possibility of hurting someone who has some set of characteristics.

The Actos drug litigation has been in the news of late. Can you give us an overview of the key Daubert ruling and argument in the Actos MDL?

This was one of the very first pharmaceutical cases where an epigenetic mechanism was identified and applied to a specific individual. There's no doubt that epigenetic data was relevant to previous cases, but decades ago, no one knew about it or emphasized it. DES cases almost surely had epigenetic mechanisms at play and indeed that's been argued in recent cases involving DES. Many pesticide cases and other chemical cases probably involved epigenetic mechanisms, but we didn't at the time have the appropriate tools to shed light on them.

What was unique about the Actos case is that a group of plaintiff's experts were able to show an epigenetic mechanism that would explain the manner in which tumors could quickly arise in particular persons. The experts were able to show a path by which the tumor could appear quickly, within a year of exposure. And that a tumor like this could only occur through this type of mechanism. So again, it's looking at a specific pathway by which genes and proteins can operate in a particular person and then show changes in the expression of proteins from their DNA (an epigenetic change) and the potential consequence: a rapidly occurring tumor.

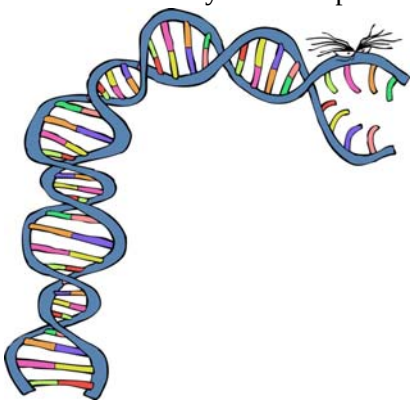
In the Actos MDL ruling, you see the legal system moving away from broad epidemiological studies and instead focusing on particular molecular pathways and individuals to find a specific effect that's operating through an epigenetic mechanism. This is the first time I'm aware of that an approach like this has been applied so effectively. And it was very powerful and effective because there was not a debate about what the studies could mean. To be sure, there were arguments on both sides but the MDL judge said there plainly was enough evidence for the plaintiff to create issues for a jury to decide after hearing from some world class experts.

Doesn't this decision seem to fly in the face of the classic view that you need controlled epidemiological studies to establish causation?

Right, it's moving the bar. Even if the exposure doesn't cause the condition in all or most people, it may be that it did cause the disease in a particular person.

So, does this approach support the view that future cases might establish causation based on genomic and epigenetic mechanisms?

Exactly. So, for example, there's a mutation called the *Kras* mutation that's involved with a lot of cancers such as lung cancer. There was a very interesting study published in *Nature* this January showing that when lung cancer is caused by a chemical mutation – as opposed to a spontaneous mutation – it has a very different profile. So you can now look at a lung cancer and see whether it is a chemically caused lung cancer or a spontaneous lung cancer or a lung cancer with some other cause.



That's revolutionary. You're starting with the actual patient and the molecular profile for their disease—whether it's cancer or some other disease—and then moving backwards.

There was a recent paper published by Tomasetti and Vogelstein that seemed to have caught everybody's attention. What are your views about the significance of the paper, and did they get it right?

I think it is very significant. We used to look at tumors as a homogenous group, but we now see that there's a big differences between tissues and even within tissues in terms of what causes them. Tomasetti and Vogelstein found a huge difference in tumor rates between different tissues, based on the rate of cell proliferation. And we know that there are agents that cause cell proliferation—any agent that causes any kind of tissue irritation, for

example, is going to result in cell proliferation and, in turn, will increase your cancer risk.

One way to look at this is across *tissues*, but you can also look at it across *people*. If someone is getting exposed to something that's causing constant irritation of their lungs or stomach, that's very likely to result in cell proliferation, which is going to increase their cancer risk. That is very important from a litigation perspective.

The other issue that is important from a litigation perspective is the paper's demonstration that some cancers—perhaps a majority of these cancers—are caused by chance. That's what the big media splash was all about. Now, that conclusion was very important because it goes to the issue of specific causation. If it's a particular type of cancer, for example, and there's a chemical agent that has been identified that may cause that cancer in *some* people, it's important to be able to know that it *was not* caused by the chemical in other people. The hope is that we will be able to use these molecular techniques to compensate those people in whom the chemical *did* cause the cancer and to not compensate those people in whom the chemical *did not* cause the cancer. That would be a much more just legal system.

This thinking, supported by this paper, bolsters the idea of a paradigm shift in the litigation system, which now recognizes that there are differences between tissues and exposures and between individuals.

So, according to their theory, it's possible that you may be exposed to a cancer-causing chemical and that you may have the appropriate genetic makeup but that you might, by good luck, not get cancer.

That's right. It's a very luck-based stoichiometric process that determines whether or not you get a mutation or other epigenetic change that sparks a tumor. We all have thousands and thousands of tumors in our body right now, as we speak. The question is: "Who are going to be the unlucky ones who will develop these tumors far enough to kill or injure them while they're still alive?" Again, from a litigation perspective or a justice perspective, what we want to do is to compensate those individuals who have tumors that were caused by specific exposures.

There is a whole academic debate in criminal law about the "lucky" defendant, or the culprit who shoots a gun in a crowd but doesn't hit anybody whereas another guy shoots a gun and he *does* kill someone. Aren't they equally blameworthy? But one got lucky and the other did not.

That's a fascinating question in the criminal arena, and it's similar to the issue we face in the toxic tort arena. If you are a "lucky" plaintiff, in that the chemical *did* cause your tumor, then you *should* get compensated. If you are an "unlucky" plaintiff, in that the chemical *did not* cause your tumor, then you *should not* get compensated.

So, from a defendant's perspective, even if you, as a company, didn't look into it properly, if your chemical *did not* cause the cancer, you shouldn't be liable.

Some have written that these new genomic techniques might bring back certain older litigations such as thalidomide, DES, and others. What do you think about that possibility?

Yes, there's a lot of potential litigation that just isn't viable right now because this exposure might cause two percent of an illness in a given population. You could never show specific causation with our current techniques, or you could never show that an exposure increased the risk of disease using epidemiological techniques.

With these genomic techniques you're going to be able to look, with a much more fine-tuned method, at the individual level and find that there are, in fact, some people that the agent actually harmed. A current example is the case of thimerosal and autism, where a number of well-conducted studies have shown that vaccines do not cause autism. But there's also a gene out there that a few people have that may predispose them to a greater susceptibility to mercury. Courts are now looking at that

gene and saying that if you don't have the gene, there is no way you can go forward, but if you do have the gene, maybe you can. So, if scientists can identify these "susceptibility genes" in some individuals, these cases may become viable again and actually have empirical support.

This raises a broader issue: Is it the duty of a company to protect every single person or just the average person? As we get more information, we're going to find cases where people could not collect in the past because the court system was overwhelmed by people that weren't affected, or perhaps we didn't even know that there were some affected individuals because we didn't have enough precision.

So I do think it's possible that we'll get more of these cases. We'll also get the potential for more multi-generational cases, such as DES, because of the multi-generational impacts of genetic mutations and also epigenetic effects. That's going to create numerous issues. For example, if your great-grandfather was exposed to a pesticide, can you bring a lawsuit if you can show that this chain of epigenetic changes was transmitted down? That's going to open up a whole new area of potential liability.

Two litigation areas that seem to be highlighted the most in association with genomic techniques concern asbestos and benzene. Do you agree with this, and if so, why do you think that is?

My view is that the reason that you're seeing the greatest interest in genetics in these areas is that those are some of the biggest areas of litigation. I believe that almost any agent is going to have a genetic component that will become important in the future. The problem is that it is difficult to get the right data, the right people working on it, the proper funding, and a number of good, high quality studies.

Benzene and asbestos are such major socially recognized, well-known carcinogens that there's a lot of work being done on them—and there's a lot of litigation. So it seems to take a critical mass to make the genetic stuff come forward just because it's worth developing that wealth of knowledge. As it becomes easier and easier to apply these types of genetic techniques, I see this awareness spreading to all kinds of hazardous agents. So, I don't think there's necessarily anything unique about these two agents; it's just that they are the focus of major toxic torts, so it makes sense that these techniques would be applied.

Benzene is one agent that can cause different types of leukemia, but there are many other things that can do this as well. It turns out that chromosomal changes can be a landmark, an indicator of whether benzene was the cause or whether it was caused by something else. That's why these techniques have so much currency in the courtroom. But it's going to be the same for *most* agents that can cause cancer and have other effects. We just don't have the science yet.

The same goes for asbestos, where differential susceptibility is an issue. Defense attorneys are looking for an argument to demonstrate that the mesothelioma *was not* caused exclusively by asbestos. And now that a mutation has been identified supporting that susceptibility, this approach may be valid. It's important to keep in mind that there are susceptibility mutations for *every* chemical. It's just a matter of time before those concepts are better understood, developed, and deployed in the courtroom. So, in my view, asbestos and benzene are two early toxic torts where genomic information is being used because they're such important areas of litigation. However, moving forward, these techniques will be relevant for any type of person with this type of toxic tort litigation.

Do you see any changes or increased attention from the judiciary right now in terms anticipating these issues, perhaps the getting together of new statutes or other rules of evidence?

No. This is interesting because I've given many talks to judges about this and they're interested in it because they've started to see cases involving these genomic issues. But I haven't seen anything in terms of new rules of evidence or anything like that. I was on the National Academy of Sciences Committee a few years ago and we put together guidelines for handling these issues, but there is nothing in the legal system that I am aware of.

There are many important social, political, and ethical issues relevant to learning about an individual's genetic

information. Interestingly, most of the rules we have don't apply in the litigation context, for example, we have HIPAA privacy rules in general and, specifically, the Genetic Information Non-Discrimination Act (GINA) that generally don't apply here.

There are really interesting debates going on in the medical context amongst health-care providers about the kinds of duties they will have to patients. Because when you have entire genome sequences, you get all kinds of information and findings that were not the major focus of your investigation. These unanticipated findings could have profound implications for an individual's medical future, so doctors and medical societies are debating the duties of a doctor to disclose this information to the patient, who may or may not even want to know it. Nevertheless, it's important information that could affect the patient's future health.

So, what's going to happen in the litigation context? We're finding out this information and none of the statutes, such as HIPAA or GINA, apply. It's not really a health provider- or doctor-patient relationship, rather, we're now getting information about someone's genetic makeup that could have profound implications that go far beyond a particular legal case.

On Saturday, I was on a panel with a doctor who was a defense expert. In the course of litigation, he saw some information that may have been important to the person's future health. He ended up talking to the judge, who instructed the plaintiff's lawyer to tell his client about this risk. I think that we're going to see this sort of issue arising more and more. There are the recent guidelines given to doctors by the American College of Medical Genetics that state that if you genetically sequence someone and you find one of fifty-six different genes, you are required to tell him about it and counsel him on what it means.

What's going to happen in a litigation context? Will the judge instruct the legal team to counsel the plaintiff about relevant genetic information? We're clearly unprepared to deal with these issues.

What is the impact of all this information on "duty to warn"?

I was recently at a conference, and we were trying to determine whether a company has a duty warn about genetic risks because we know that people are going to respond differently to different exposures, based on their genetic makeups. For example, we already have warning labels on diet sodas stating that they contain phenylalanine and that this chemical can be a risk to certain genetic subtypes: specifically, individuals with phenylketonuria (PKU).

So there's already a product that has been labelled for genetic risk, but it's a risk that the people with that condition will always know about because it will be detected at birth. The problem is that people don't know their genotypes, so there's no sense in warning them. However, as we continue to get more and more of this genetic information over the coming decades, we're all going to have that information and the duty to warn people of a particular susceptible genotype is going to be a huge issue. The question is: if you don't, will you be liable and/or will you suffer punitive damages?

So, what about damages?

The issue of damages is fascinating. For example, maybe a defendants will use genomic techniques to assess whether a woman has a BRCA gene in order to predict that her life expectancy is going to be diminished and therefore they would be liable for lower damages. Conversely, plaintiffs may turn around and attempt to predict increased longevity based on an individual's genetic makeup and therefore argue that they are entitled to more damages.

Will these techniques be used to quantify exposure?

Quantifying exposure is a huge issue in these cases. Sometimes courts are letting in exposure estimates without really good evidence, and other times plaintiffs are being thrown out of court because they can't quantify their exposure, even though that exposure may well have caused their disease. So basically, your genes are going to be the single best dosimeter available. They monitor and change in response to your chemical environment. That's becoming increasingly clear. There's still much work that needs to be done to hone these tools so that they're good enough to be used to use in specific legal cases. However, there is good reason to believe that these will be excellent tools for quantifying exposure.

How are juries supposed to digest these complicated scientific concepts?

There have been studies and mock studies done with juries and with judges, and they actually do a pretty good job of understanding this information. Maybe juries are a little bit too quick to jump to conclusions, but judges are becoming more and more educated on these topics.

I think it's the attorneys that are really dropping the ball. This information and these techniques should be used much more than they are. Many attorneys I talk with tell me that they didn't study science and that they are simply not ready to jump in on this, but I think that there are numerous cases right now where this type of approach is right.

We're now getting examples of where these approaches are valid and useful, and you know, sometimes you can still win a case with imperfect science. Our legal system is not a strict scientific system. Whether it should be or shouldn't be is a great question for debate, but the reality is that it's not perfect. So even when the science is not quite fully there, why not give it a try and put some of this evidence in.

What do you think is the scientific discipline that's best suited to addressing some of these questions, either as a consultant or as a testifying expert?

I think it's going to be a combination, but I'd have to say that it would be a molecular geneticist who understands tumor etiology and can look at a specific tumor and basically try to characterize what likely caused it. This individual has the expertise that is going to be the most effective and useful because it addresses the question of specific causation.