

Epigenetic research offers potential for biomarkers and mechanistic understanding of suicide

Infinium™ microarrays enable high-throughput analysis of molecular mechanisms underlying complex psychiatric conditions



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Both external and internal factors can influence epigenetic changes to DNA, altering gene expression and biological states. Research suggests that these types of epigenetic factors may play a key role in psychiatric disorders, including suicidality.¹

Marie Gaine, PhD, is an Assistant Professor in the College of Pharmacy at the University of Iowa. Her lab is investigating epigenetic markers of suicidality and bipolar disorder. We spoke with her about her research and the potential it has for people with mental illness.

Q: What originally drew you to epigenetics and its role in suicide and bipolar disorder?

Marie Gaine (MG): From the time that I first learned about epigenetics, it always fascinated me. If we consider genetics to be what we get from our parents, that doesn't really change. However, epigenetics is exciting because these marks are dynamic throughout our lifetime. Sometimes, it can even be reversed, making it a potential therapeutic target.

I started my research career looking at epigenetics in cancer, but I quickly realized that cancer wasn't where I wanted to keep my focus. So I began postdoctoral studies looking at suicide epigenetics research and immediately fell in love with it. This was also partly because I was lucky enough to start when researchers first began recognizing that suicide was a biological dysfunction in the brain. At that time, everything was novel, and epigenetics was at the forefront.

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Q: What do we know about the relationship between epigenetics and psychiatric disorders?

MG: My lab studies the epigenetics of psychiatric disorders in two ways. First, we look at potential mechanisms where epigenetics could be changing biological pathways in the brain that could be associated with increased risk. The second avenue of research is studying epigenetic changes in easily accessible samples, such as blood, for potential biological markers for people that might be at increased risk. My work aims to discover biomarkers that may help identify individuals in vulnerable populations and identify dysregulated molecular mechanisms linked to suicide.

Q: How can methylation biomarkers help with suicide research?

MG: We can already administer questionnaires, so I do get asked about the need for biomarkers for suicide. I would argue that there's still a lot of stigma surrounding suicide. A lot of people don't want to talk about it and there are a lot of vulnerable populations that have a significantly increased risk, like individuals with bipolar disorder. Epigenetic research provides additional tools and insights that can benefit this group that we know are at high risk.

Q: How does your work contribute to or challenge existing thinking in your field?

MG: Some of my recent work has focused on looking at the interplay between genetics and epigenetics. I am interested in how SNPs or other genetic variants might influence methylation in the context of patterns associated with suicide.^{2,3}

It's something that we as a field are only now able to consider because it's costly to generate genetic and epigenetic data together. However, I have been able to show that there are patterns that are associated with suicide, so if you have a particular SNP alongside a specific methylation signature, you could have a significantly increased risk compared to either factor alone.^{2,3} I think as the field moves forward, we're going to start using that type of evidence to combine genetics and epigenetics research.

Q: What kinds of samples do you typically use?

MG: Our lab mainly uses blood samples. Through my collaborations here at the University of Iowa and around the world, I have access to a large number of blood samples, including some longitudinal samples that are over 20 years old, which are exciting to analyze. Because we are looking for biomarkers, it is important to use easily accessible samples, and studies have shown that blood-based methylation patterns can serve as a valid proxy for neurobiological processes even when blood is not the primary tissue of interest.⁴

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Q: How do collaborations play a role in advancing your research?

MG: Collaborations are a huge component of my research, allowing me to do validation and replication of my work. For example, I have a collaborator at the University of Texas Health Science Center, in Houston Texas, who has conducted similar research to mine using Infinium MethylationEPIC arrays and blood samples from individuals with a combined history of bipolar disorder and suicide.^{5,6} Collaborations also provide opportunities for multidisciplinary projects such as combining methylation and brain imaging data,⁷ which would not be possible with my lab alone.

Q: Why did you choose to work with Illumina microarrays to advance your research?

MG: During my postdoctoral research, I worked with postmortem brain samples, which had obvious benefits because it's the organ of interest, but there were also significant limitations. One of the major limitations for methylation analysis is that it's very hard to get the number of brain samples needed to correctly identify changes in methylation. Also, with postmortem brains, tissue fixation can introduce molecular changes that can affect accurate methylation analysis.

For these reasons, when I started my own lab, I really wanted to change my sample type to something more accessible. This led us to look at blood samples and that's the main reason I started using Illumina microarrays. Using blood samples with the 96-sample kits allows us to robustly and quickly generate data from a large number of samples. Currently, we can generate data for 96 samples in three days.

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Because so many researchers use these types of arrays, one major benefit is that there are already well-established R tools available to analyze the data. For example, one of my papers examines epigenetic aging using CpGs that are covered in the MethylationEPIC array.⁵ The available tools allow us to easily run clock analyses or metabolomics analyses. It's now a general rule of thumb that when people join my lab they learn R to analyze methylation data.

Q: What unanswered questions or future directions do you find most exciting as you look ahead?

MG: My lab has gradually been moving towards female-specific research topics, which I find especially compelling. We currently have funding to look at methylation patterns during pregnancy, and it was surprising to me that we don't know a lot about epigenetics during pregnancy. We do know that methylation changes because the whole body changes to prepare for birth and motherhood, but not a lot of studies have looked at the specific methylation patterns, especially those that are related to brain changes.

We're also really interested in psychiatric disorders that can arise during pregnancy. Suicide is a leading cause of death during the peripartum period.⁸ For that project, we have a collaboration with a research group in Sweden to look at methylation associated with suicidal ideation during pregnancy. I have high hopes for this project and we already have a publication under review that uses DNA methylation changes in early gestation to predict suicidal ideation postpartum.⁹

Q: In five years, what would success look like for your research, and for psychiatric disease research more broadly?

MG: My goal is to reduce the stigma of suicidality in vulnerable populations. Finding mechanisms could help change this by showing suicide is something that has gone wrong with the biology of your brain, and not something you did wrong. Demonstrating that methylation patterns change with suicidality is my five-year goal.

I've also talked a lot about biomarkers. I don't think we're going to be there in five years. Having an assay would be an awesome goal but there are also a lot of ethical implications with doing any sort of blood test for psychiatric disorders. We don't want to have false positives and there are important privacy concerns.

I think moving the field forward in any way in five years would be meaningful. For example, we're starting our own blood collection in pregnant women that could be a valuable resource for future research.

Q: What advice would you give to students or early career researchers who are interested in pursuing work in epigenetics or psychiatric diseases?

MG: There are so many promising research directions right now. I would say that one thing that the next generation of students should be thinking about is mechanisms. There are a lot of research projects out there like mine that are generating large DNA methylation datasets without figuring out why methylation patterns are changing. I think that is the most obvious direction that the field is headed—figuring out the mechanisms underlying methylation patterns. Mechanistic work is, in my view, one of the most important directions for the next generation of researchers, particularly given how central medication response is currently practiced in psychiatric care.

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Learn more

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