Pamela Sklar

(1959–2017)

Psychiatrist who sought the genetic roots of mental illness.

When most researchers could not remotely conceive of how to do it, Pamela Sklar's mission was to elucidate the genetic underpinnings of mental illness. A psychiatrist and neuroscientist, she was determined to pursue a systematic analysis of the human genome in search of insights that could help the millions of people globally who battle conditions such as schizophrenia and bipolar disorder.

Sklar was pivotal in pushing forward the idea that many such conditions are polygenic: they result from small effects in many genes, rather than just one or a few. The view — controversial and unproven even 10–15 years ago — transformed psychiatric research. It promoted the understanding that some mental illnesses are no different from complex physical diseases that involve many genes. Sklar's founding and leadership of research consortia were crucial in making the first genetic breakthroughs in these areas. She died on 20 November 2017.

Sklar was born in 1959 in Baltimore, Maryland. During high school, she studied piano at the Peabody Institute in Baltimore, and she enjoyed playing all her life. She earned a bachelor's degree in classics and philosophy from St John's College, a liberal-arts university in Annapolis, Maryland, in 1981.

Sklar showed an early passion for science and medicine. She spent summers working in labs and studying chemistry at Johns Hopkins University in Baltimore; she subsequently earned both her medical degree, in 1985, and her PhD in neuroscience, in 1988, there. Sklar worked in the lab of Solomon Snyder, who revealed the mechanisms of psychotropic and antipsychotic drugs. She did a residency and postdoc work in psychiatry at Columbia University in New York City, with molecular biologist Richard Axel, who in 2004 shared the Nobel Prize in Physiology or Medicine. In 1995, she married molecular biologist and geneticist Andrew Chess, with whom she had two children. She moved to the Massachusetts General Hospital in Boston in 1997.

Sklar was instrumental in founding a psychiatric-genetics programme in 2004 at the then-nascent Broad Institute of MIT and Harvard in Cambridge, Massachusetts. There, in 2007, she helped to launch the Stanley Center for Psychiatric Research. In 2011, she moved to the Icahn School of Medicine at Mount Sinai in New York City and founded the Division of Psychiatric Genomics. It was there that she spent the rest of her career.

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Sklar recognized early on the magnitude of the challenge of looking for mental illness's biological roots. Until the past decade, most psychiatric-genetics research used approaches that were successful in the 1980s and 1990s for rare disorders such as Huntington's disease, cystic fibrosis and muscular dystrophies. These techniques sought single genes with strong causal mutations.

By the late 1990s, the lack of success of these efforts in the field of psychiatry revived a long-hypothesized alternative model. Several influential reviews and pilot studies began to explore the idea that some diseases might result from the combined effects of hundreds or thousands of DNA variants, with each genetic variant having a small effect on individual risk. By the mid-2000s, technological advances and the human variation patterns emerging from the Human Genome Project made it possible to explore this hypothesis for the first time.

Sklar realized that the same technologies that were crucial to finding genetic risk factors for diseases such as diabetes could be applied to mental illness. Testing these hypotheses would require huge numbers of willing patients and healthy volunteers. But there was no infrastructure in place for sharing genetic and clinical information globally, and even the idea faced resistance. As a result, Sklar was pivotal in founding what evolved into the Psychiatric Genomics Consortium. She also led and contributed to the first International Schizophrenia Consortium in 2006, and early bipolar-disorder consortia.

In 2009, a seminal publication delivered by these efforts and led by Sklar changed thinking on schizophrenia — and psychiatric diseases as a whole (International Schizophrenia Consortium *Nature* **460,** 748–752; 2009). It reported the first statistically robust evidence that inherited risk variants for schizophrenia were indeed polygenic; the results came from genome-wide association studies. The study also revealed that bipolar disorder and schizophrenia share many genetic risk factors — further supporting other hypotheses about the molecular underpinnings of mental illness.

Critics posited that the lack of strong 'acting' variants suggested that the approach had missed important heritable factors, or that the polygenic patterns were artefacts.

Sklar and her colleagues were undaunted. In 2014, another study definitively established more than 100 distinct risk factors for schizophrenia — cementing the concept (Schizophrenia Working Group of the Psychiatric Genomics Consortium *Nature* **511,** 421–427; 2014). The field is now beginning to learn how to read the many biological clues uncovered, and to pursue them in research into other mental illnesses.

Pamela was an unwavering advocate for the importance of genetics research in improving the lives of those with schizophrenia and bipolar disorder. Throughout her career, she was on the right side of every important decision in our field, whether regarding data sharing, mentorship or in supporting the interests of younger researchers. She led by word and by example — and even through her final months, the passion with which she pursued her research inspired all of us.

She was a fantastic and dedicated mentor to many, and an idol and passionate advocate for women in science. I am proud that Pamela was the first collaborator to welcome me into the psychiatric-genetics community, nearly 20 years ago. Her legacy lives on in the progress we have made, and in the brighter future for people battling mental illness. ■

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