

Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

Noboru Hiroi: Exploring the cellular and developmental origins of neuropsychiatric disorders linked to human copy-number variation

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Professor Noboru Hiroi is a faculty member in the Departments of Pharmacology, Cellular and Integrative Physiology, and Cell Systems & Anatomy at the University of Texas Health Science Center at San Antonio (UT Health San Antonio), USA. He joined his current institution in 2019 after working at Albert Einstein College of Medicine in New York for 21 years. His current work is focused on the cellular and developmental origins of the dimensions of neuropsychiatric disorders in genetically engineered mouse and cell models. Professor Hiroi is happy to provide our readers with reflections on his life and career.

Part 1: Noboru Hiroi – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was born in a small town near the port city of Yokohama, Japan. It is surrounded by mountains and the ocean, and there is rich animal life. I was always fascinated by the normal and abnormal ways animals behave. As an undergraduate student at Waseda University in Tokyo, a lecturer who spent his sabbatical year at McGill University (Montreal, Quebec, Canada) taught me about the discoveries by James Olds and Peter Milner of a reward center in the rodent brain, D.O. Hebb's conceptualization of synaptic plasticity, and multiple memory systems by Brenda Milner and Norman M. White at McGill. I was fortunate to receive a full scholarship from a newspaper company in Japan and, later, another scholarship from the Government of Canada to complete my PhD at McGill. These first pivotal events set the stage for my career in science.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

My PhD thesis work was focused on the anatomical loci critical for amphetamine's addictive properties. After completing my PhD thesis in 1991, I was offered postdoctoral positions in labs that were working on anatomical substrates of addictive substances at the University of British Columbia (Vancouver, British Columbia, Canada), Cambridge University (Cambridge, United Kingdom), and the Massachusetts Institute of Technology (MIT, Cambridge, MA). I chose the laboratory of Professor Ann M. Graybiel at MIT to expand my graduate training in behavioral neuroscience to the compartmentalization of the striatum, a field pioneered by Dr. Graybiel and others. At MIT, I was involved in a collaborative project with Dr. Susumu Tonegawa, one of the pioneers who introduced genetically engineered mice in studies of the role of genes in behavior. I completed a second postdoctoral program in the laboratory of Dr. Eric Nestler at Yale University (New Haven, Connecticut, USA) to further develop my skills in the molecular analyses of addictive behaviors in genetically engineered mouse models. My work there involved determining the roles of two genes, FBJ murine osteosarcoma viral oncogene homolog B (*FosB*) and dopamine- and cyclic adenosine monophosphate-regulated phosphoprotein, Mr 32 kDa (*DARPP-32*), in genetic knockout mouse models, in



Figure 1. Noboru Hiroi, PhD, University of Texas Health Science Center at San Antonio, USA.

collaboration with Dr. Michael E. Greenberg at Harvard and Dr. Paul Greengard at Rockefeller University.

I was recruited to Albert Einstein College of Medicine in New York in 1998 as an independent junior faculty member to further strengthen its addiction research program. However, I was soon fascinated by my colleagues' work on patients who carried copy-number variants (CNVs) at human chromosome 22q11.2. Patients with these CNVs exhibit schizophrenia, intellectual disability, and autism spectrum disorder at rates far above what is expected in the general population. It became apparent that these patients represented genetically identifiable cases of mental disorders, which was too interesting a topic to pass on, and I started a new project exploring this association in 1999. My postdoctoral training in the integrative use of genetically engineered mice enabled me to contribute to the work of Einstein's 22q11 research team. I was fortunate to collaborate with many 22q11 pioneers, including Drs. Raju Kucherlapati, Bernice Morrow, and many others.

As my mouse work developed, I started expanding the level of analysis by forming a team of investigators specializing in the imaging of mouse brains, computational modeling, and cell models. This collaborative team grew to involve many investigators outside Einstein, including groups in Ireland and Japan. I currently organize an international team with those investigators.





What kind of impact do you hope to achieve in your field by focusing on your specific research topics?

I hope to increase the knowledge of cellular and molecular substrates for 22q11.2 CNV-linked psychiatric disorders so that the implementation of precision medicine in psychiatry can become a reality.

Could you tell us more about your current scholarly focal points within your chosen field of science?

My current point of focus is to elucidate and finely define the cellular and developmental origins of cognitive deficits commonly affected in CNV-associated cases of schizophrenia, autism, and intellectual disabilities. The ultimate validation of our findings in cell and mouse models would come when therapeutic options developed from the mechanistic understanding derived in these model systems prove to be effective for treating highly specific dimensions of mental disorders, which would be my dream. Even if potential therapeutic options turn out to be not effective, the negative outcomes would further motivate me to explore other potential cellular and developmental mechanisms of mental illness in model systems.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your own research environment?

From my thesis mentor, Norman M. White, I learned to stick to my own ideas, even when they are not well accepted. I learned scientific rigor from Ann M. Graybiel and the importance of visions from my collaboration with Susumu Tonegawa at MIT. I learned cutting-edge molecular approaches from Eric Nestler at Yale. From all of my major scientific mentors, I learned the importance of continuously incorporating new techniques and ideas into my project.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

The current trend, which I do not particularly appreciate, is that articles consistent with prevailing dogmas tend to populate major high-impact journals and those inconsistent with these prevailing dogmas are not published in prominent journals. This trend is exacerbated by the geographic locations of the authors. Authors who do not reside in countries where dogmas are popular might be published less frequently, if the reviewers of their work are from countries where the dogmas are widely held. I am passionate about promoting work that does not support the prevailing concepts.

What do you most enjoy in your capacity as an academic and research leader?

The most enjoyable moments are the times when I discuss new ideas with my colleagues.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

My mother is housed in a care facility in Japan that specializes in Alzheimer's disease. Whenever I have a chance, I try to fly to see her.

Part 2: Noboru Hiroi – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

For me, perfect happiness involves seeing that kind of happiness in my family and two dogs.

What is your greatest fear?

My mother is currently afflicted with Alzheimer's disease. The prospect of developing the same condition at some point in my life is currently my greatest fear.

Which living person do you most admire?

There are too many to pick a few.

What is your greatest extravagance?

My greatest extravagance involves sharing superb Japanese food with my colleagues and collaborators.

What are you most proud of?

I am trying to achieve this state of mind about my work by the time I die or cease to function intellectually.

What is your greatest regret?

I tend to forget what I regret.

What is the quality you most admire in people?

One of the most admirable qualities in people is their ability to achieve goals despite adversity. I gave my son the middle name Moses. You get the idea of what qualities I admire in people.

What do you consider the most overrated virtue?

I am not sure. It depends on certain perspectives, and they differ individually.

What is your favorite occupation?

My current occupation is my favorite. This job is what I dreamed of as a child.

Where would you most like to live?

I would live anywhere I can collaborate with good people until I develop dementia or retire. After retirement or developing dementia, I would most likely live in Japan to enjoy the great food and hot springs. Moreover, Japan offers good, affordable medical care and care facilities. Major surgeries and good care facilities in the United States would cost me a fortune.

What is your most treasured possession?

I do not treasure physical possessions. Seeing my father's belongings after he recently passed away made me realize that physical possessions do not mean much. I cannot "possess" nonphysical things. My family is not my "possession." Therefore, I cannot think of any treasured possessions.

When and where were you happiest? And why were so happy then?

I am happiest now. I have never been this happy. Relatively speaking, my life was not so great earlier.

What is your most marked characteristic?

I tend to speak honestly and frankly, even to the extent that my speech may be blunt and abrasive at times.

Among your talents, which one gives you a competitive edge?

I tend to say what I think is true, even if it makes others uncomfortable or infuriated. That is the only thing I can think of, if you count it as a talent.

¹ In the late nineteenth century various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions aim to provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.



What is a personality/characteristic trait you wish you had?

I do not wish to have something I do not have or am incapable of having.

What do you consider your greatest achievement?

My greatest achievement so far is that I have survived as a researcher.

What do you most value in your friends?

The attributes I most value in my friends are that they are forgiving and not judgmental.

Who are your favorite writers?

I enjoy many nonfiction writers.

Who are your heroes of fiction?

I don't like heroes in fiction or fictional worlds. I do not like Disney or any other theme parks that include heroes. If anything, I prefer villains. They are tough.

Who are your heroes in real life?

Heroes in real life are those who sacrifice everything for the benefit and well-being of others.

What aphorism or motto best encapsulates your life philosophy?

The essence of life described in Ecclesiastes best encapsulates my life philosophy. Despite its seemingly pessimistic view of life, its conclusion is

that one should nevertheless pursue wisdom because that is what providence dictates.

Noboru Hiroi¹

¹*Departments of Pharmacology, Cellular and Integrative Physiology, and Cell Systems & Anatomy, UT Health San Antonio, San Antonio, Texas 78229, USA*

e-mail: hiroi@uthscsa.edu

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