

Takeo Yoshikawa: Exploring the biological underpinnings of psychiatric disorders, such as schizophrenia, through genetics and metabolic insights

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Dr. Yoshikawa currently serves as the Administrative Director of the RIKEN Center for Brain Science in Japan. His journey with the institution began in 1999 when he assumed the Principal Investigator (Team Leader) role and established the Laboratory of Molecular Psychiatry. Before this, he gained experience at various esteemed institutes, including the Department of Psychiatry at Tokyo Medical and Dental University, the National Institute of Physiology in Japan, and the National Institute of Mental Health (NIMH) in the USA. For 22 years, Dr Yoshikawa dedicated himself to unraveling the molecular intricacies of psychiatric diseases within his laboratory. Transitioning to his current position, he now lends his expertise to the operational endeavors of the Center. Beyond his administrative responsibilities, Dr. Yoshikawa actively engages with the academic communities, serving as a grant reviewer, scientific advisor, and editorial board member for scientific journals. Remarkably, he maintains his clinical practice, caring for patients as a psychiatrist. Dr Yoshikawa graciously participated in the Genomic Press interview, sharing insights into his life and career and providing valuable reflections for our readers.

Part 1: Takeo Yoshikawa – Life and Career

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

As a young child, my insatiable curiosity led me to incessantly pepper my late father with questions about the world around me. Remarkably, he always had an answer ready. While my father harbored the aspiration of becoming a researcher, the uproar of WWII steered him toward a career in teaching instead. Undoubtedly, his influence played a notable role in shaping my professional journey. Initially drawn to the complexities of physics and chemistry, I pursued my studies at the University of Tokyo. However, the growth of molecular biology in the 1970s stimulated my interest, prompting me to delve deeper into the field of biology at Osaka University Medical School. During my undergraduate tenure, I seized the opportunity to immerse myself in immunology, dedicating my spare hours to research under the guidance of Professor Tadamitsu Kishimoto, whose groundbreaking work included the discovery of IL-6 and its receptor. Despite my immersion in the intricacies of immunology, I gravitated toward psychiatry as graduation approached. Its enigmatic nature at the time intrigued me deeply, and I sensed untapped potential within the field. Additionally, perhaps subconsciously, I was drawn to psychiatry for reasons that will become clearer as I delve further into my narrative.

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?

I completed my psychiatry training at the Tokyo Medical and Dental University. During that period, there persisted a prevailing sentiment of anti-psychiatry, and research into the biological underpinning of mental

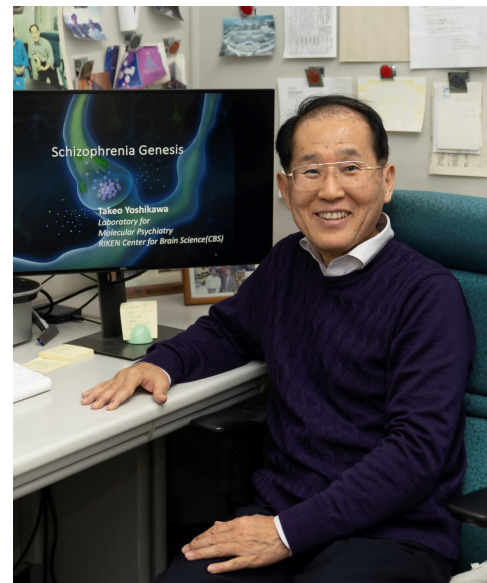


Figure 1. Takeo Yoshikawa, MD, PhD, RIKEN Center for Brain Science, Japan.

illness was often dismissed. However, I embarked on psychopharmacological research, focusing on the CCK peptide, a neurotransmitter known to coexist with dopamine. My endeavors centered on elucidating how antipsychotics and psychotomimetics regulated CCK levels.

I was driven by an unwavering quest to understand the fundamental origins of mental disorders and recognized the necessity for a comprehensive understanding of neuroscience. Consequently, I joined the esteemed laboratory of Professor Kunihiro Obata at the National Institute of Physiology in Japan. Professor Obata had made groundbreaking discoveries regarding GABA as an inhibitory neurotransmitter in the central nervous system. In this new environment, I delved into investigating the molecular mechanism underlying the phenomenon of amphetamine-induced behavioral sensitization in rodents, an established animal model for schizophrenia.

Please share with us what initially piqued your interest in your preferred area of research or professional focus.

While in animal research, I sensed a notable divergence between animal models and human psychiatric disorders. By the late 1980s, some researchers began performing linkage analysis to approach the causes of psychiatric disorders more closely, sparking my interest in the human genetics approach. In 1993, I seized the opportunity to join the Neurogenetics Branch of NIMH under Dr Elliot Gershon's leadership, where intensive linkage analysis of bipolar disorder was conducted. Working under





Dr Sevilla Detera-Wadleigh, a thoughtful mentor and exceptional researcher, I delved into genetic analysis. I consider myself fortunate to have crossed paths with her.

What were the key impact areas of your research topics?

Upon my return to Japan, I was able to establish my laboratory at RIKEN in 1999. There, I initiated a nationwide consortium aimed at gathering DNA samples for schizophrenia and other psychiatric disorders, making the commencement of our genetic studies. From the late 1990s to today, we have found ourselves amidst an exhilarating era characterized by remarkable advancement in human genetics, spurred by numerous technical and conceptual breakthroughs. While acknowledging the potency of genetics as a formidable tool, it has become increasingly evident that mental disorders exhibit extreme polygenicity. They manifest as disruption in gene expression precipitated by an amalgamation of multiple risk variants and epigenetic alternations. My laboratory has undertaken various approaches using human-derived materials to elucidate potential therapeutic interventions and yield actionable insights. These include conducting postmortem brain studies and engaging in research involving induced pluripotent stem cells (iPS).

Could you tell us more about your most relevant focal points within your chosen field of science?

Although I did not initially realize it when I embarked on my journey into psychiatry, my research journey may have been influenced by a notable experience I had as a teenager: an intense episode of depersonalization. This ordeal proved to be formidable and challenging, exacerbated by the lack of effective medication available at the time and even now. Driven by a fervent desire to comprehend the mechanisms underlying mental disorders, I have recently developed a novel hypothesis. I propose that energy metabolism within the brain plays an essential role in mental illness. Specifically, I hypothesize that excessive hydrogen sulfide production may impair energy metabolism, leading to what I term "reductive stress." Consequently, I am inclined to shift the focus of my research toward exploring the anti-inflammatory mechanisms triggered by "sulfide stress" rather than solely adhering to the conventional inflammatory theory of psychiatric illness. This approach holds particular significance for disorders such as schizophrenia, which I view as a progressive and fundamentally complex disease process.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you have maintained throughout your life?

If I struggle to navigate challenges and experience distress, it may signify that my approach is still tentative. However, by delving deeper into my thoughts and contemplating more extensively, I can uncover clues that will guide me toward a solution. This principle holds not only in the realm of science but also in personal life.

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 you think warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

The Internet has enabled the free sharing of resources, yet it has recently underscored English speakers' advantage in spreading scientific results. In numerous countries, particularly developing regions, it would be best for individuals to pursue scientific studies in their preferred language. The evolution of artificial intelligence (AI) presents a partial solution to this issue. I am hopeful that future progress will lead to improvements in this regard.

What have you most enjoyed in your capacity as academic or research leader?

I have found immense joy in my academic journey, navigating the challenges of psychiatric research with a foundation in clinical psychiatry and basic biology. Equally gratifying has been the opportunity to nurture a

spirit of teamwork among my laboratory staff, united in our pursuit of a common goal. Witnessing their career growth has been a source of great satisfaction.

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?

I cherish the opportunity to travel alongside my wife, indulging in leisurely drives and unwinding in soothing hot springs known as "Onsen." Additionally, I derive immense pleasure from loading my bicycle into the car and venturing to the outskirts for cycling excursions on my days of respite.

Part 2: Takeo Yoshikawa – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

I find true fulfillment when I become completely engrossed in my thoughts, allowing myself to forget everything else around me.

What is your greatest fear?

I am accustomed not to dwelling on things too deeply. I believe that everything unfolding in our world, even in the vast expanse of the universe, is intricately intertwined with destiny.

Which living person do you most admire?

I deeply admire and am grateful to my laboratory staff, who worked tirelessly together toward our common goal.

What is your greatest extravagance?

My wife and I own a second house located 600 km away from our residence, which my wife's parents previously inhabited. One of my indulgences is embarking on journeys up the highway to visit them occasionally. We enjoy staying there, immersing ourselves in the tranquility of country life and reveling in the beauty of the surrounding nature.

What are you most proud of?

I have been fortunate and proud to pursue what I truly desire, largely due to my wife's unwavering support and dedication.

What is your greatest regret?

I refrain from dwelling on thoughts of the past.

What is the quality you most admire in people?

Compassion and empathy toward others.

What do you consider the most overrated virtues?

Every individual possesses unique virtues and strengths, each of which holds immeasurable value and significance.

¹In 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. In 2003, Proust's handwritten answers were auctioned off for \$130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Spike Lee, 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 provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**What is your favorite occupation?**

Engaging in research endeavors and associated tasks, alongside providing consultation to patients.

Where would you most like to live?

I currently reside in Japan and immensely enjoy it. I relish the beauty of four distinct seasons and abundant natural landscapes. However, the region is prone to frequent natural disasters.

What is your most treasured possession?

What holds the utmost value for me are the friendships I have built.

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

In Japan, there is a saying that "misfortune and fortune are like the strands of a rope, intertwined." It is important to remain cautious during times of prosperity to preserve hope during adversity.

What is your most marked characteristic?

While I may tend to prioritize my desires, potentially inconveniencing others, I make a concerted effort to collaborate and cooperate with them whenever possible.

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

A personality that endeavors to approach things slightly differently from others.

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

I cannot change my inherent nature, so I am content with who I am, but I acknowledge that I could benefit from cultivating a much sharper sense of humor.

What do you consider your greatest achievement?

The public stigma surrounding mental illness in Japan was notably potent. It would bring me immense satisfaction if I could have played a minor role in reducing this stigma by advocating for research into the biological aspects of mental disorders.

What do you most value in your friends?

Trust and integrity.

Who are your favorite writers?

Yasushi Inoue, the renowned Japanese writer, resonates with my mindset.

Who are your heroes of fiction?

There are many heroes to admire in Japanese manga. However, I am particularly drawn to individuals who, despite not being overly intelligent, possess a genuine and flawed humanity.

Who are your heroes in real life?

My parents and my wife.

What aphorism or motto best encapsulates your life philosophy?

If one dies after being enlightened about the true path, one has not lived in vain.

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