

Genomic Psychiatry

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INNOVATORS & IDEAS: RESEARCH LEADER

C. Robert Cloninger: Mechanisms and conditions by which temperament, character, and personality development can regulate health and well-being

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Dr. C. Robert Cloninger's contributions have been foundational in understanding temperament, personality, and their biological and genetic underpinnings. Cloninger explored how temperament, character, and personality traits are influenced by genetic factors and how they predict various psychological disorders, such as alcoholism and personality disorders. His prospective studies involving adoptees reared apart from their biological parents provided crucial insights into the heritability and development of personality traits independent of environmental influences. Moreover, Cloninger's pioneering work in conducting the first genome-wide association and linkage studies of normal personality traits laid the groundwork for subsequent research in psychiatry and behavioral genetics, linking specific genetic profiles to patterns of temperament and personality. He is also the creator of two extensively employed personality assessment instruments: the Tridimensional Personality Questionnaire (TPQ) and the Temperament and Character Inventory (TCI). Dr. Cloninger serves as Director of the Anthropedia Institute and Professor Emeritus at Washington University in St. Louis, where he studies the biopsychosocial foundations of personality that influence health and illness. The Anthropedia Institute is the research branch of the Anthropedia Foundation, a non-profit organization dedicated to the promotion of human well-being through initiatives in health care and education. He served as Wallace Renard Professor of Psychiatry & Genetics, Professor of Psychological and Brain Sciences, and founding Director of the Sansone Center for Well-being at Washington University until July 2019. Dr. Cloninger is a member of the National Academy of Medicine USA, Fellow of the American Academy for Advancement of Science, and an editor of various journals in psychiatry, psychology, and genetics. We are pleased to share Dr. Cloninger's answers to the Genomic Press Interview.

Part 1: C. Robert Cloninger – Life and Career

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

Learning about nature and living things has always fascinated me. Among my fondest childhood memories are exploring forests and streams, where I observed wildlife, collected insects, and enjoyed immersion in nature. I loved gardening with my grandfather and discussing character development with my mother, an actress who directed the local community theater, and my father, who taught literature. I arranged to enroll in schools with the best available science curriculum because by age 10, I planned to become a medical doctor. In high school, I loved all math and science, especially biology and chemistry. My first taste of research came while in high school during a National Science Foundation college program in biological sciences. At the University of Texas (UT) in Austin, I was in the Plan II Honors Program, studying philosophy, anthropology, and psychology in addition to pre-medical courses. For my honors thesis at UT with the anthropologist and science fiction writer Chad Oliver, I examined the



Figure 1. C. Robert Cloninger, Anthropedia Institute and Washington University in St. Louis, USA.

worldview of William Golding to ask questions about the nature of a good and healthy life. I also worked as a research assistant doing operant learning experiments, but I found these theories needed to be revised to explain human capacities for awareness, as considered in my studies of phenomenology with philosophers Irwin Lieb and John Silber. Decades later, I was able to test these various views of human learning capacities in research on the science of well-being.

I picked the research-intensive Washington University (WU) School of Medicine (WUSM), where I began research with psychiatrists Samuel Guze and Eli Robins, doing both laboratory and clinical research that was influential in the development of DSM-III and IV. At each step there were mentors and colleagues who helped me develop and deepen my insights.

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

Where I trained, the Department of Psychiatry at WUSM emphasized direct measurement of categories with little use of psychodynamic or motivational hypotheses. Nevertheless, Sam Guze was receptive when I suggested that we could begin hypothetico-deductive research to understand why antisocial personality disorder and somatization disorder often occur in the same individual and the same families. By studying female criminals and their family members, we found that both disorders shared familial predispositions, but for women to become antisocial required a stronger predisposition than men. After finishing my residency, I continued that approach in longitudinal studies of psychiatric outpatients and





their families, developing expertise in clinical assessment and differential diagnosis.

Then, I applied new quantitative genetic techniques to the family data I had collected with Guze and Ted Reich. Ted's new analytic methods allowed us to systematically test hypotheses about alternative inheritance models, which I found satisfying. From 1975 to 1978, I developed models of combined genetic and cultural inheritance using path analysis at WU. In 1978-79, at the University of Hawaii, I extended those models with geneticists Newton Morton and DC Rao in consultation with Sewall Wright. We were awarded a succession of NIH grants at WU that allowed us to put together a creative multidisciplinary group, eventually resulting in my leading a Clinical Research Center in Psychiatric Genetics.

I continued to try to understand the role of personality in the patterns of comorbidity in psychiatric disorders. However, I found that the assessment techniques in psychiatry for personality disorders needed improvement, particularly those restricted to directly observed behavior without considering motivational processes within the person. I studied the psychometric methods of leading personality theorists whom I met through sociologist-epidemiologist Lee Robins, including Ray Cattell, Hans Eysenck, Jeffrey Gray, Robert Hare, and Daisy Schallings. However, I had no formal theory about personality structure until 1986, when two events converged. Beginning in 1980, I conducted adoption studies of alcoholism and related psychiatric disorders in collaboration with Michael Bohman in Sweden. We found personality variables to be associated with risk for alcohol abuse and related behaviors. Then, in 1986, I was invited to describe the factors differentiating susceptibility to generalized anxiety and somatization. To explain this, I developed my theory of temperament dimensions (Cloninger, 1987), drawing on operant learning theory as the underlying basis for behavioral conditioning of temperament in a model that accounted well for personality disorder subtypes.

Soon, I found that a behavioral conditioning model of temperament alone could not account for whether an individual was mature or not. I vividly remember the moment when I was faced with the temperament profiles of two men with nearly identical temperament scores: one was a violent criminal, whereas the other was a responsible and civilized executive. This forced me to develop my model of character as a moderator of temperament in 1993, reawakening my early interests in the humanities and phenomenology.

The combined model of temperament and character provided a comprehensive description of personality needed to diagnose whether someone had a personality disorder (based on character) and what subtype they had (based on temperament). It also predicted associations with physical and mental health disorders and levels of well-being (physical, mental, and social). Together with psychiatrist Dragan Svravic and his twin brother, physicist Nenad Svrakic, I investigated the dynamics of personality change in longitudinal studies, confirming in 1997 that, if there was a change, we could predict what changes would occur in a self-organizing adaptive system. However, it remained unclear what conditions were needed to elicit personality change.

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

The dearth of empirical information about the mechanisms and conditions by which personality development can regulate health and well-being indicated a need for leadership to establish an integrative, multidisciplinary center to understand the underlying mechanisms of personality development as a complex adaptive system or, more fully, as a multi-modular network of complex adaptive systems. A Center for Well-being was endowed for this purpose under my leadership at Washington University in 2001. Shortly after that, in 2004, a large group of scientists, educators, and physicians formed the non-profit Anthropedia Foundation to develop educational programs for training coaches and therapists with a strong understanding of the role of personality in the biopsychosocial and spiritual aspects of health and well-being.

My book *Feeling Good: The Science of Well-being* described the initial foundation for a transdisciplinary approach in 2004. I described the broad roots of a science of well-being in scientific fields from physics, chemistry, and genetics to psychology, sociology, and philosophy. This allowed for the

consideration of biopsychosocial processes, from molecules to cells, organs, and organ systems in the body, and on to society, the planet, and the cosmos. Fortunately, interest in the use of the TCI was strong around the world, and the Centers for Well-being at WU and the Anthropedia Foundation have been able to organize international collaborations to study the science of well-being with a highly multidisciplinary team using innovative methods in well-characterized data sets. The team includes psychiatrists, psychologists, anthropologists, neuroscientists, geneticists, and experts in bioinformatics and artificial intelligence, with data from many cultures around the world, as summarized in recent articles on genomics (Cloninger & Zwir, 2022), transcriptomics (del Val et al., 2024), and related studies of all aspects of health (physical, emotional, cognitive, social, and spiritual).

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

Just as the quantum revolution led to a paradigm shift in physics in the early 20th century, the epigenetic revolution has spurred a paradigm shift in the 21st century (Cloninger, 2004; del Val et al., 2024). There is growing evidence that all life forms involve complex information-processing networks that are self-organized as specialized functional modules that interact collaboratively to turn one another on and off to adapt to changing external and internal conditions. Our collaborative team just completed the first study of the transcription of the whole genome in relation to human personality. We found that human personality orchestrates gene expression networks for neuronal plasticity, epigenesis, and adaptive functioning that influence all aspects of physical, mental, social, and spiritual health. We are pioneering ways to extend methods that have previously been restricted to experimental animals to humans in ways that are non-intrusive and beneficial, such as identifying the fundamental changes at a deep molecular level that underlie changes in gene expression and brain connectivity in response to increased awareness from interventions that promote health and well-being.

Please tell us more about your current scholarly focal points within your chosen field of science

We aim to investigate epigenetic change during personality development further by studying chromatin modification and by longitudinal studies of transcriptomics and brain connectivity before and after therapeutic interventions for a range of clinical syndromes and disease spectra.

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

In my experience, the most effective habits and values for academic studies are the same temperament and character traits that promote health and well-being in general: complex systems for reliability, resilience, and creative self-awareness.

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 well-being of scientists influences their productivity, integrity, and creativity. Well-being is impaired when people strive to publish from extrinsic pressures (such as fear or to profit personally) rather than from intrinsic drives to uncover what is accurate and beneficial for society. Science has not been immune to the increasing pressure to compete for money for profit like a business rather than to function as a community of mutually respectful scholars seeking greater awareness of truth to benefit individual and collective well-being.

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

I enjoy developing new methods to test hypotheses that previously could not be investigated by bringing together experts and approaches from



multiple disciplines. The satisfaction comes from the experience of helping all members of the team to develop their skills and share in the generation of increased awareness of what is accurate and beneficial for all.

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?

For leisure around home, I enjoy gardening, hiking in nature, reading, and discussions with friends. I like to travel to other countries and cultures with their diverse rituals, traditions, and cuisines (which is a benefit of international research!).

Part 2: C. Robert Cloninger – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Happiness is the enduring satisfaction that comes from service to others, letting go of all struggles and complaints, and growing in awareness. It is not seeking transient pleasures, which stimulate insatiable and self-defeating desires.

What is your greatest fear?

I fear that humanity is responding inadequately to the existential threats to civilized life as we know it. We are postponing the kind of creative response that has allowed us to survive prior urgent threats over the past 100,000 years.

Which living person do you most admire?

Sherry Lee Cloninger, an artist and my wife, confidante, and best friend.

What is your greatest extravagance?

My passion for Mediterranean and Maghrebian cuisines.

What are you most proud of?

My family and friends.

What is your greatest regret?

I appreciate music and regret never learning to play a musical instrument. I had the opportunity as a child but refused because I preferred to play outdoors. I could have managed to do both.

What is the quality you most admire in people?

Wisdom, which comprises all the virtues.

What is the trait you most dislike in people?

Cruelty.

What do you consider the most overrated virtue?

Pride (because the lack of humility is not self-respect or a sense of intrinsic dignity).

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, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, 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?

What I am doing now is what I most love to do.

Where would you most like to live?

Along the Mediterranean coast of Europe because of the culture, cuisine, and climate.

What is your most treasured possession?

Mementos of my family, friends, and our activities together.

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

Here and now because I have learned to enjoy life as a journey of constant learning in which there are always more wonders and mysteries to discover.

What is your current state of mind?

I am happy and thankful for what I have experienced and learned. I am enthusiastic about the amazing scientific tools we now have to better understand the world. I am hopeful for the future for myself and others despite many serious situations in the world that may cause many people to endure suffering. I view such suffering with compassion rather than fear because I have faith in the unconditional resilience of life itself.

What is your most marked characteristic?

My generous friends say it is creativity and intellectual curiosity. To me, it is just a willingness to be open-minded about what is possible and to put those ideas to the test.

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

The combination of interpersonal insight with analogical reasoning (to see commonalities between familiar and novel sets of relationships) and synthetic reasoning (to integrate elements of information into a new whole). This combination generates new ideas from available information to be critically examined and refined by further experience. Resilience and persistence also help.

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

I wish I were more patient, particularly when interrupted while working.

What do you consider your greatest achievement?

Development of the Temperament and Character Inventory (TCI).

What do you most value in your friends?

Good humor, kindness, and candor so that we can balance serious reflection with playfulness.

Who are your favorite writers?

Plato, Immanuel Kant, Mahatma Gandhi.

Who are your heroes of fiction?

The resourceful and clever leader *Odysseus* and the practical and wise mentor *Athena* (both in Homer's *Odyssey*).

Who are your heroes in real life?

Joseph and Genoveffa Mazzagatti (my kind and intelligent grandparents, Italian immigrants to the USA. They taught their extended family to love learning and discovery of the wonders of nature); and *Sewall Wright* (a founder of population genetics who developed path analysis and the analysis of complex adaptive systems in genetics and evolution. At age 7, he wrote his first book, *The Wonders of Nature*, and then continued to publish scientific works until he died in 1988 at age 98. Wright was a Unitarian who recognized the irreducibility of consciousness to matter, as did



Spinoza and philosopher Charles Hartshorne, a close friend of both Wright and my other mentor at UT, Irwin C. Lieb).

What aphorism or motto best encapsulates your life philosophy?

Be the change you wish to see in the world.

C. Robert Cloninger¹ 

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