

Guy A. Rouleau: Genetic foundations of neurological disease – From risk variants to pathogenic mechanisms

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In this engaging Genomic Press Interview, Dr. Guy A. Rouleau, OC, OQ, FRCPC, FRSC, FAAN, opens up about his remarkable journey from a young boy conducting chemistry experiments in his basement to becoming Director of The Neuro (Montreal Neurological Institute-Hospital) and Chair of McGill University’s Department of Neurology and Neurosurgery. A world-renowned clinician and neurogenetics researcher, Dr. Rouleau has dedicated 35 years to uncovering the genetic foundations of devastating neurological conditions, identifying dozens of disease-causing genes in ALS, hereditary neuropathies, epilepsy, schizophrenia, and autism. His scientific impact is reflected in nearly 1,000 peer-reviewed publications cited over 110,000 times, but his vision for transforming research methodology may be his most lasting legacy. As co-founder of the Tanenbaum Open Science Institute and First Vice-President of the World Federation of Neurology, he is pioneering a revolution in scientific collaboration by establishing The Neuro as the world’s first academic institution fully committed to open science principles. Through personal anecdotes and professional insights, Dr. Rouleau shares his passion for sailing, commitment to mentoring the next generation, and unwavering belief that open, collaborative science will accelerate discoveries to benefit patients worldwide.

Part 1: Guy A. Rouleau – 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 fell in love with science when I was a child. It began when I attended the local university’s science day, which was aimed at children—it worked. In no time, I was building a chemistry lab in my basement and doing all kinds of experiments. By age 10, I knew I would be a scientist. I had my first explosion at 12 years old. The workings of the universe, from chemistry to outer space, fascinated me.

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?

There are a few defining moments that oriented my career. As an undergraduate in biochemistry at the University of Ottawa, I was told by my professors that there was no future in science and that I should go into medicine, which I did. Medicine is a great field, and I love it. However, while doing my residency, I felt the urge to return to science and research. The next defining moment was when I did a neurology rotation with Dr. Albert Aguayo, a very successful physician scientist at McGill University. I decided that this was my future – to become a physician-scientist in the field of neurology, like him. When I was finishing my neurology residency, I was looking for the field of research I should embark on. Dr. Aguayo sent me to see his friend, Dr. Martin, who was then head of neurology at Harvard, who strongly suggested that I enter the field of genetics, and he



Figure 1. Guy A. Rouleau, MD, PhD, McGill University, Canada.

suggested a lab for me at Harvard. I followed his great advice and joined the lab he suggested. After my postdoc and PhD, I returned to McGill on faculty and pursued my career as a physician-scientist. The last defining moment came many years later when my brother became Dean of Medicine at the University of Montreal, and he convinced me to join him there in a leadership position in neuroscience. I greatly enjoyed this role as it allowed me to build research teams in cutting-edge fields. Over the next few years, I recruited over 100 professors, first to the University of Montreal and then to McGill University (Figure 2).

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

When I started working as a postdoc at Harvard, I discovered the field of genetics. It was absolutely fascinating, and I loved learning as much about genetics as I could. In fact, I decided to stop my postdoc after one year and become a graduate student so that I could take many of the excellent advanced courses in genetics that were offered. It was an amazing time!

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

Ultimately, I hope that my discoveries will have a meaningful impact on people’s lives. First, they will allow accurate diagnosis and genetic counseling, and ultimately, they will lead to new, effective treatments.





Figure 2. Home of groundbreaking discoveries: The iconic Montreal Neurological Institute-Hospital ('The Neuro'), where Dr. Rouleau has helped build one of the world's leading neuroscience research centers. The historic architecture houses cutting-edge research, perfectly embodying the institute's blend of tradition and innovation. Note the 'neuro' signage atop the building – “even on cloudy Montreal days, neuroscience shines bright.”

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

I am focusing on a few neglected but prevalent diseases that significantly affect quality of life: essential tremor and restless legs syndrome. I continue to try to understand the pathogenesis of amyotrophic lateral sclerosis and develop new treatments for this devastating disease.

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

The lab where I trained was really a dog-eat-dog cutthroat lab. I vowed that I would never let that happen in my lab, so I worked hard to keep the environment healthy and with as few conflicts as possible. As for my values, I am completely honest and share everything I have—something I learned early in my career, not always by example.

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?

I have come to believe that science must be done in an open fashion. We must be honest and generous and freely share our data and reagents in a timely manner. Competition has value, but it must be done in an open manner. As a postdoc, I witnessed horrible behaviors that could only be bad for science. We need to embrace open science.

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

I most enjoy interacting with my students. Their successes are an endless source of joy, and I am very proud of them.

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 am happiest when I am in a boat sailing in some interesting part of the world. Or canoeing on a river or a series of lakes in the wilderness with my wife. Both of these activities reenergize me.

Part 2: Guy A. Rouleau – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

Sailing with my wife and close friends in an interesting part of the world (Figure 3).

What is your greatest fear?

My greatest fear is failing at something important to me.

Which living person do you most admire?

My brother Paul.

What is your greatest extravagance?

My obsession with sailing eats up tons of money and time!

What are you most proud of?

Having managed to succeed in many spheres of life, despite many obstacles.

What is your greatest regret?

Not having focused my work on a more limited number of problems.

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.



Figure 3. Joy at the helm! A perfect day of sailing, showcasing Dr. Rouleau's greatest passion outside of science. Here he demonstrates that while genetic research may be complex, sometimes happiness is as simple as a blue sky, open water, and a steady breeze.

What is the quality you most admire in people?

Honesty.

What is the trait you most dislike in people?

Authoritarianism.

What do you consider the most overrated virtue?

Assertiveness.

What is your favorite occupation (or activity)?

Sailing and all that comes with it: seamanship, navigation, being able to fix anything.

Where would you most like to live?

The south of France.

What is your most treasured possession?

Pictures of my family.

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

During the pandemic, I retreated to my country home in the forest. I hiked in the forest every day (sometimes on snowshoes!), always surrounded by nature. I did my work efficiently but in a marvelous setting.

²Marcus Aurelius, *Meditations* (Book 12.17) (Latin: "Si non rectum est, ne feceris; si non verum est, ne dixeris.").

What is your current state of mind?

Happy.

What is your most marked characteristic?

Determination.

Among your talents, which one(s) give(s) you a competitive edge?

Curiosity: always thinking out of the box. And perseverance: never giving up.

What do you consider your greatest achievement?

Having contributed to the training of many, many students over the years.

If you could change one thing about yourself, what would it be?

I would like to be more extroverted and adventurous with respect to human activities, like going out more.

What do you most value in your friends?

Loyalty and honesty.

Who are your favorite writers?

Isaac Asimov, J.R Tolkien, and Edgar Rice Burroughs.

Who are your heroes of fiction?

Sherlock Holmes, and Tarzan.

Who are your heroes in real life?

Nelson Mandela, Mahatma Gandhi, and Albert Einstein.

What aphorism or motto best encapsulates your life philosophy?

"If it is not right, do not do it, if it is not true, do not say it." – Marcus Aurelius.² Or, paraphrasing Warren Buffet: "don't do anything you would not want to be on the first page of the *New York Times*."

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