



# Profile of Jean-Laurent Casanova

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Jean-Laurent Casanova. Image courtesy of John Abbott (photographer).

In January 1972, weeks before she turned four, Marie-Dominique Martin was rushed to a clinic in Nevers, a manufacturing town that sits plumb in the middle of France in the picturesque Burgundy region. For more than two months, Martin had suffered a bewildering array of symptoms, including fever, fatigue, hip and abdominal pain, and difficulty walking. Blood tests indicated inflammation, and X-rays revealed a lesion in the right thigh bone. As her condition worsened, she was admitted to Claude Bernard Hospital in Paris, where a biopsy and a battery of tests revealed multiple bone lesions reminiscent of microbial infection.

Six months earlier, in the fall of 1971, Martin had received the mandatory Bacille Calmette–Guérin (BCG) vaccine against tuberculosis (TB). The vaccine, a live but defanged strain of the TB bacterium, is perfectly harmless in nearly all children and crucial to protection against childhood TB. Months after vaccination, however, Martin had developed signs of infection around the inoculation site on her arm. Based on an array of clinical tests, pediatrician Nicolas Thomassin in Nevers and his colleagues at Claude Bernard surmised that disseminated bone inflammation triggered by the live vaccine might be the reason behind the child's symptoms. "My parents thought I was not going to make it," recalls Martin. But, as Thomassin expected, a mix of antibiotics, targeted against BCG, helped treat her condition, and she returned home symptom-free after almost nine months of care. The unassuming subtitle of Martin's case report, recounted in a little-known French outlet in 1972, was an unobtrusive nod to the medical team's collective puzzle: *difficulties of an etiologic diagnosis*. It took nearly three decades for the underlying cause of her illness to be finally unveiled.

The summer of 1994 was marked by a frenzy of letter writing for Jean-Laurent Casanova, a plucky young resident at the renowned Necker Hospital for Sick Children in Paris. Casanova had become fascinated with reports in the medical literature of otherwise healthy children who became severely ill with disseminated BCG infection. Following a hunch that such children might

be genetically predisposed to their puzzling ailments, he sent off letters to hundreds of pediatricians across France, soliciting case reports. When Thomassin received Casanova's letter, he hastened to respond with an account of Martin's case. Before long, Martin, who was then 27 years old and went by the married name Devainon, arrived at Necker to consult with Casanova.

Six years later, Casanova laid bare the genetic basis of Devainon's immune deficiency in punctilious detail. The findings, which eventually led to a career spurt for Casanova, now an immunologist at the Rockefeller University in New York City, exemplify his insights on inborn errors of immunity. For these insights, Casanova has earned coveted honors, notably Belgium's InBev–Baillet Latour Health Prize, Germany's Robert Koch Award, France's Sanofi–Pasteur Award, and membership in the US National Academy of Sciences.

## Passion for Pediatrics

Casanova was born in Paris just a few years before the 1968 riots that mark a cultural moment in the city's storied history. Although his family included philosophers, scholars, lawyers, and businessmen, there were no scientists among his close kin. Nor do the ham radios, chemistry sets, and amateur microscopes that so often pepper the potted biographies of scientists figure in the story of his formative years. Instead, Casanova simply says, his choice of medicine after high school was driven by a deep-rooted instinct to pursue a field of study crucial to human well-being. "I can't explain it. It's similar to someone knowing they want to be a locksmith or a pilot or something else. I wanted to become a physician-scientist, and I felt compelled to do it."

Reckoning that medical training would shore up his prospects should his scientific career fail to soar, he enrolled at the Cochin Medical School at the University of Paris Descartes in 1981. Seven years later, as a medical resident with a Master's degree in life sciences earned along the way, Casanova began doctoral studies in molecular biology at the Pasteur Institute. A chance encounter with a visiting postdoctoral fellow from the Ludwig Institute for Cancer Research in

Lausanne, Switzerland, sparked a partnership, paving the way for a PhD in molecular immunology, which he completed in Lausanne in 1992. Soon thereafter, he returned to his residency in Paris, convinced that his calling as a physician-scientist pivoted on pediatrics and immunology. In 1995, he joined pediatrician Claude Griscelli at Necker Hospital as a clinical research fellow, soon became the principal investigator of a small research team in immunology, and began work that augured a career unraveling inborn errors of immunity.

Casanova's interest in the subject stemmed from his experience treating children afflicted with infectious diseases, in particular the rare children who became severely ill after receiving the live but attenuated BCG vaccine, which has been proven to be otherwise safe and effective. Following a long and frequent tradition of medicine inspiring research, Casanova wondered whether these puzzling observations might have a genetic basis.

## Rendezvous in Paris

So when Devainon's blood sample arrived at Necker in 1994, Casanova's team combed through it for a genetic link. Through gene sequencing, Casanova found that Devainon harbored a mutation in a gene switch called STAT1, which activates genes involved in immune response against mycobacterial infections. Although her parents carried two normal copies of the gene, Devainon and her two children each carried one mutant copy, predisposing them to disseminated mycobacterial

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page E7118.

infection upon exposure to an otherwise safe and essential vaccine. Compared with cells from healthy individuals, Devainon's immune cells mounted a weak response when stimulated with the immune molecule interferon (IFN) gamma, which helps fend off mycobacteria. The findings, published in *Science* in 2001 (1), laid to rest a decades-long mystery that had perplexed Devainon's family and physicians, reinforcing the vaccine's intrinsic safety and uncovering a genetic basis for the rare syndrome now known as Mendelian susceptibility to mycobacterial disease.

Recalling her 1999 meeting with Casanova at Necker, Devainon, now 47, says, "I am grateful that he brought clarity to my childhood illness and gave it a name. We were relieved to learn that it was a genetic defect so we could take precise steps with my children."

Around this time, Casanova met Laurent Abel, a physician in Paris with a penchant for epidemiology, and the pair bonded over their mutual interest in the genetic underpinnings of infectious disease, approaching the subject with complementary skills. Casanova's team performed the experiments, while Abel furnished the computational insights that enabled them, their formidable synergy resulting in a lifelong research partnership.

By 1999, Casanova had briskly scaled the ranks to become professor and head of the laboratory of human genetics of infectious diseases at Necker, and after nearly a decade of spadework in the field, was invited to move to Rockefeller University in New York City. The preeminence of the university in his area of interest and the prominence of the city as a cultural capital of the modern world proved strong enticements. "Rockefeller is an institution at which not only many Americans but also several Europeans have made major contributions in the fields of immunology and infectious disease. And New York today is like London was in the 1900s and Paris in the 1800s, which made the offer hard to resist for a Parisian," says Casanova. In 2008, Casanova moved to Rockefeller with most of his experimental team; Abel continues to lead the laboratory's Paris branch, overseeing computational efforts on both sides of the Atlantic.

Following the tack he took with mycobacterial disease, Casanova and colleagues next explored the genetic basis of chronic mucocutaneous candidiasis, a condition marked by repeated or recalcitrant infections of the skin, nails, oral, and genital mucus membranes with the normally harmless fungus *Candida albicans* in children with otherwise normal immune systems. The focus of these studies was, among others, a French child of Moroccan origin who had suffered bouts of dermatitis

shortly after birth and at five years of age. Scanning the child's genome, Casanova's team uncovered an array of genetic mutations that converged on a type of immune response mediated by so-called Th17 cells. These cells secrete the immune molecules IL-17A and IL-17F, which, it turned out, are crucial for human immunity against *Candida* but not other infectious agents. By contrast, previous studies had found that mice lacking these immune molecules are susceptible to a broad range of pathogens, underscoring the significance of the kind of human genetic analysis that has become Casanova's stock-in-trade. As a dividend, the findings also explained why, for example, patients with acquired immune deficiencies such as AIDS, are prone to candidiasis (2). "By focusing on specific groups of patients, we can decipher a pathogenic mechanism that has a general value in other medical settings," says Casanova. More importantly, the findings suggested that administration of IL-17A/F or molecules that act downstream in immune signaling might help treat patients with candidiasis.

#### Disease Detective

To truly establish the genetic basis of susceptibility to childhood infections, Casanova realized he needed a model unrelated to primary or acquired immune deficiencies and seemingly random in inheritance. So he set his sights on a common Western scourge—the herpes simplex virus, which triggers no more than a cold sore in most people. However, the virus can infect the central nervous system and spur herpes simplex encephalitis (HSE) in 1 of 10,000 children born every year, resulting in runaway brain inflammation, epilepsy, and death (3). To Casanova, the baffling susceptibility of such children raised the specter of a single-gene error of immunity. Since its description in 1941, the disease was not thought to run in families. Hence, Casanova reasoned, such children may harbor genetic defects with incomplete penetrance, a form of clinical manifestation that characterizes single-gene defects inherited in a non-Mendelian pattern.

Together with pediatric neurologist Marc Tardieu, Casanova and Abel conducted a survey of French children diagnosed with the disease, and found 86 patients from 52 families. In 13% of these families, the children had been born to relatives, suggesting that they likely inherited two defective copies of an unknown gene conferring susceptibility to the infection. The following years witnessed the uncovering of mutations in a protein called UNC93B, isolated from the cells of a 15-year-old French boy with HSE-related brain damage who carried two mutant copies

of the gene. Before long, other mutations surfaced, including those in an UNC93B-dependent cellular pathway that affects a signaling receptor called TLR3 that were identified in the cells of unrelated French children not born to relatives.

Further work with Harvard Medical School's Luigi Notarangelo and Memorial Sloan-Kettering's Lorenz Studer revealed that the mutations uncovered by Casanova and colleagues impaired type 1 IFN-mediated immunity to herpes simplex virus, and experiments using stem cells grown from patients' skin cells helped establish that the mutations rendered the patients' brain cells susceptible to the virus (4–6). Moreover, the seeming specificity of the children's infection suggested that TLR3 was crucial for protective immunity against the virus in the brain but redundant for immunity to other microbes. Although a clinical trial of type 1 IFN for children with HSE-related brain inflammation is yet to be launched, the findings provided physicians a rational basis for the compassionate use of IFN- $\alpha$  to treat such children.

Galvanized by these findings, Casanova explored the genetic basis of another rare condition: isolated congenital asplenia. Children with the condition are born without a spleen, which helps fight pathogens, and often require lifelong treatment with antibiotics to fend off potentially fatal infections, in particular with pneumococcal bacteria. Many cases of asplenia go undetected until after death, and the cause of the disease had long remained a mystery. Until, that is, the team, led by graduate student Alexandre Bolze, hit upon a mutant gene. Identified by sequencing the genomes of more than three dozen patients from North and South America, Europe, and Asia, the gene encodes a protein called RPSA, which forms a part of cells' protein-synthesizing ribosomes (7). Precisely why mutations in a life-sustaining cellular structure such as the ribosome selectively affect the spleen remains a puzzle, but the findings represent a step toward the development of prenatal diagnostic tests for parents at risk of giving birth to children with asplenia. More interestingly, says Casanova, mutations in many ribosomal proteins typically lead to a complex syndrome called Blackfan-Diamond anemia, which does not affect the spleen, whereas patients with RPSA mutations lack a spleen but have none of the hallmarks of the anemia. "That suggests that the ribosome may be more than a factory to make proteins, that it contributes to gene regulation," speculates Casanova.

#### Cold Comfort

From the range of infections that Casanova had explored, the theme that emerged with

clock-like regularity was clear: several childhood infectious diseases may be triggered by defects in individual genes that represent disastrous holes in the body's defensive armor. Perhaps nowhere is the theme more evident than in Casanova's studies of the common flu, which is innocuous to most people. Yet some children infected with seasonal or pandemic strains of flu viruses develop life-threatening infection, raising the possibility of a genetic mechanism at play.

The puzzling case of a two-and-half-year-old French girl who had suffered acute respiratory distress syndrome, a perilous condition triggered by unchecked influenza infection, is a case in point. Caught in the throes of a raging flu, the young girl was hospitalized for nearly three weeks in 2011, administered the drug Tamiflu, and put on a ventilator. Years after her recovery, Casanova's team set out to solve the mystery of the girl's unendurable infection. When the team glimpsed into the protein-coding portion of the girl's genome, they found different mutations in both copies of a gene called IFN regulatory factor 7, or IRF7, which controls the immune system's production of type I and III interferons, which help keep influenza viruses in check. Comparing the girl's IRF7 genes with those of her parents revealed that each parent carried one normal and one defective copy, at once explaining the parents' ability and the child's failure to fight the flu. When the girl's dendritic cells were exposed to the flu virus in lab dishes, they failed to produce IFN- $\alpha$ 2, which normally helps fight the virus. Moreover, lung epithelial cells derived from the girl's own skin cells using stem cell technology

were almost twice as susceptible to the influenza virus as cells derived from healthy people. The findings, reported in *Science* in 2015, underscored a role for IRF7 in life-threatening influenza and proffered a rational basis for the use of IFN- $\alpha$  to treat severe flu in patients with this or related genetic defects (8).

Casanova's discovery that genes can influence the outcome of flu is an incidental nod to the etymology of influenza, a disease that owes its name to a medieval belief that its onset is influenced by celestial movements. But in Casanova's telling, it is genes, among other factors, that preordain the proneness to severe childhood flu. "We now think that other children with severe influenza may harbor mutations in proteins related to IRF7," says Casanova. So the team is sequencing the genomes of children with life-threatening flu to chart the genetic architecture of flu susceptibility.

Genes have long figured prominently in the history of human infectious disease, a field rife with theories that ascribe apparent differences in individual susceptibility to infections to genetic or environmental factors. To wit, in his Inaugural Article, a wide-ranging treatise that

includes scholarly notions that shaped his own work, Casanova recalls the grim fates of Charles Darwin's and Louis Pasteur's young daughters, who succumbed to fever, despite hailing from upper middle-class families with good nutrition and sanitary homes—an enduring mystery that, he says, hints obliquely at potentially hidden genetic factors (9, 10).

Over the years, Casanova's findings have brought into sharp focus the roles of individually rare gene mutations in a handful of primary infections with different patterns of inheritance and clinical manifestations. As Casanova continues to plumb the genetic underpinnings of one potentially fatal childhood infection after another, his findings have coalesced into a cumulative wisdom on inborn errors of immunity, and his conviction that the field of childhood infections is in dire need of a coherent theory has deepened. And it is precisely toward such a theory that his efforts are now directed. "We want to test the hypothesis that severe infectious diseases of childhood are genetic—perhaps as a rule," he says.

**1** Dupuis S, et al. (2001) Impairment of mycobacterial but not viral immunity by a germline human *STAT1* mutation. *Science* 293(5528):300–303.

**2** Puel A, et al. (2011) Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science* 332(6025):65–68.

**3** Zhang SY, Casanova JL (2015) Inborn errors underlying herpes simplex encephalitis: From TLR3 to IRF3. *J Exp Med* 212(9):1342–1343.

**4** Casrouge A, et al. (2006) Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science* 314(5797):308–312.

**5** Zhang SY, et al. (2007) TLR3 deficiency in patients with herpes simplex encephalitis. *Science* 317(5844):1522–1527.

**6** Lafaille FG, et al. (2012) Impaired intrinsic immunity to HSV-1 in human iPSC-derived TLR3-deficient CNS cells. *Nature* 491(7426):769–773.

**7** Bolze A, et al. (2013) Ribosomal protein SA haploinsufficiency in humans with isolated congenital asplenia. *Science* 340(6135):976–978.

**8** Ciancanelli MJ, et al. (2015) Infectious disease. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science* 348(6233):448–453.

**9** Casanova J-L (2015) Human genetic basis of interindividual variability in the course of infection. *Proc Natl Acad Sci USA* 112:E7118–E7127.

**10** Casanova J-L (2015) Severe infectious diseases of childhood as monogenic inborn errors of immunity. *Proc Natl Acad Sci USA* 112:E7128–E7137.