The Case of the Short-fingered Musketeer

Introduction

by Russ Hodge

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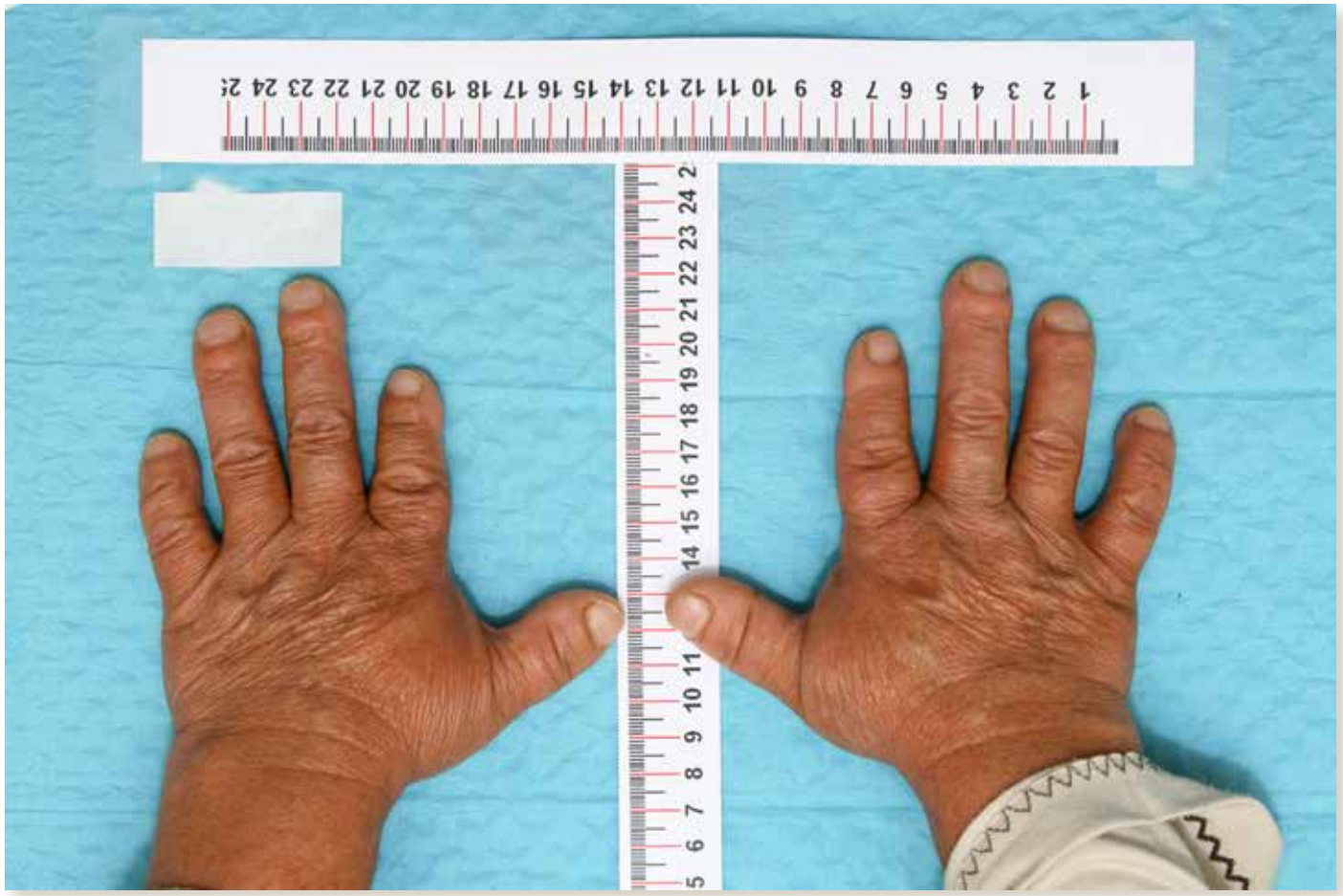
This is the story of a group of researchers searching for the causes of one of mankind's most deadly diseases. It is simultaneously the story of a Turkish family with a unique hereditary condition. A defect in their DNA gives them short fingers and toes, which is trivial, but also gives them extraordinarily high blood pressure that brings sudden death at an early age. Fifty years ago a family member set off to find a doctor who could shed light on his family's health problems. In doing so, he touched off a biomedical drama that has reached across the world and shed new light on the relationship between information in our DNA and disease.

Most science stories revolve around a mystery, and this tale has more elements of that genre than most: multiple deaths, a quest for answers that has lasted more than 50 years, a cast of characters colorful to the point of eccentricity, and the application of cutting-edge technology to a sophisticated puzzle. Appropriately enough, there were a few incidents involving firearms. And – almost – a prison break.

Over a century ago, sudden death began disrupting the peaceful existence of a family of farmers living on the Black Sea coast. Initially its selection of victims seemed random. But in the early 1960s, the family noticed a pattern and sought the help of scientists in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discovering its causes. Thirty years later, a physician and researcher named Fred Luft sank his teeth into the story and – like the best literary detectives – refused to let go. At the time he had no idea that the project might one day reveal a new mechanism by which disease arises in our cells and bodies. Or that it would require two decades to find.

It hasn't been easy going. Despite continual revolutions in biotechnology and scientists' understanding of the roles that genes play in health and disease, the answer to the puzzle has remined elusive. The lab has thrown nearly every new method and technology at the problem, but it always seems to dance away again, teasing them along. Anyone sensible would have been forgiven for abandoning the project long ago. That surely would have happened without an unusual amount of persistence on the part of the scientists and extraordinary efforts on the part of the family in Turkey. So this is a story about the human side of research: in particular about a man who has continued to inspire and motivate colleagues and students despite opportunities for frustration at every turn.

The case is a "what-dunnit" rather than a "who-dunnit," with ripe pickings for a storyteller. In the early years, it was cited as an exceptional attempt at what is now called "molecular medicine." But there has never been any guarantee that the ultimate answer to the riddle would be very meaningful or interesting. And three years ago, when the research for this book began, a definitive answer to the family's health problems was still missing, which made it a mystery story without a final chapter.

As this book appears, however, the situation is rapidly changing through a paper just published by Fred's lab in the *Journal of Clinical Investigation* and another that the group is about to submit for publication soon. The story that has appeared involves a related case and doesn't, therefore, answer every question – making this more like a real-life crime story than a literary one. Despite the loose ends, the new study brings a satisfying conclusion to this edition of the book. Soon there will need to be an updated final chapter, and maybe more than one. Finally, the case is breaking open.

Even without such a temporary resolution, the story is an apt parable for the last half-century of biomedical research. In the early 1960s, as a Turkish Imam set out to find a reason for his family's health problems, James Watson and Francis Crick were setting off for Sweden to receive a Nobel Prize. With the discovery of the structure of DNA, they had solved an age-old mystery by identifying the substance that genes were made of. Their work contributed to an explosion of new kinds of biotechnology, and just about all of it has, in some way or other, been applied to the family's strange condition. Until now, these attempts have raised more questions than answers. Yet Fred Luft's lab has persistently followed the story wherever it might lead, and in doing so, the group has acquired the reputation of mavericks.

Part of their motivation lies with the fact that hypertension, or high blood pressure, is one of mankind's greatest silent killers. It has a hydra-like nature that rears its head in many tissues, across the body as a whole. Once things get rolling, one organ system crashes after another. Finding causes for such ailments inevitably requires looking at humans in a holistic way, as extraordinarly complex systems that cover a spectrum of scale from tiny molecules to our bodies as a whole, but limitations in technology and other factors have made it impossible to truly link these levels. Imagine trying to conduct a stakeout of a house using only a microscope and the Hubble space telescope, and you'll get the idea. The biomedical equivalent of a pair of binoculars, covering the mid-range, has been missing.

For decades, scientists have known that inheriting particular forms of genes can increase the risk that a person

Fred Luft

will develop hypertension and many other diseases. In some cases the genes remain enigmas; finding them often requires looking in the most unlikely places. In this case, the place has been a family of Turkish farmers who have inherited at least two unusual and seemingly unconnected traits.

I first heard of the short-fingered musketeer in Fred Luft's office in a clinic in a suburb of Berlin, amidst neatly stacked journal articles, printouts of experimental data, and other artifacts of active research. Fred, a German-American, is a physician and a specialist in nephrology and cardiovascular disease.

I had come intending to write an article about his research activities. The week before he had sent me a few papers about a project to find genes linked to high blood pressure. At first glance the work resembled other studies of human genetics going on across the globe. There was no hint that it would take me to a distant country and become a personal adventure. Fred, on the other hand, might have predicted it – the same thing has happened to everyone else connected to the project. They all say two things: that Fred is a remarkable scientist and teacher, and that taking part in this project has had a huge impact on their lives.

Fred first heard the story 20 years ago from a colleague who had come across an obscure paper in the medical literature. That article had been written in the 1970s by a Turkish pediatric physician and geneticist named Nihat Bilginturan. He, in turn, had learned of the case from a family that appeared on his hospital ward one day with a curious tale. They were farmers from Northern Turkey, and they had the story first-hand – they were living it. A mysterious ailment was picking them off, unexpectedly, just as they reached middle age.

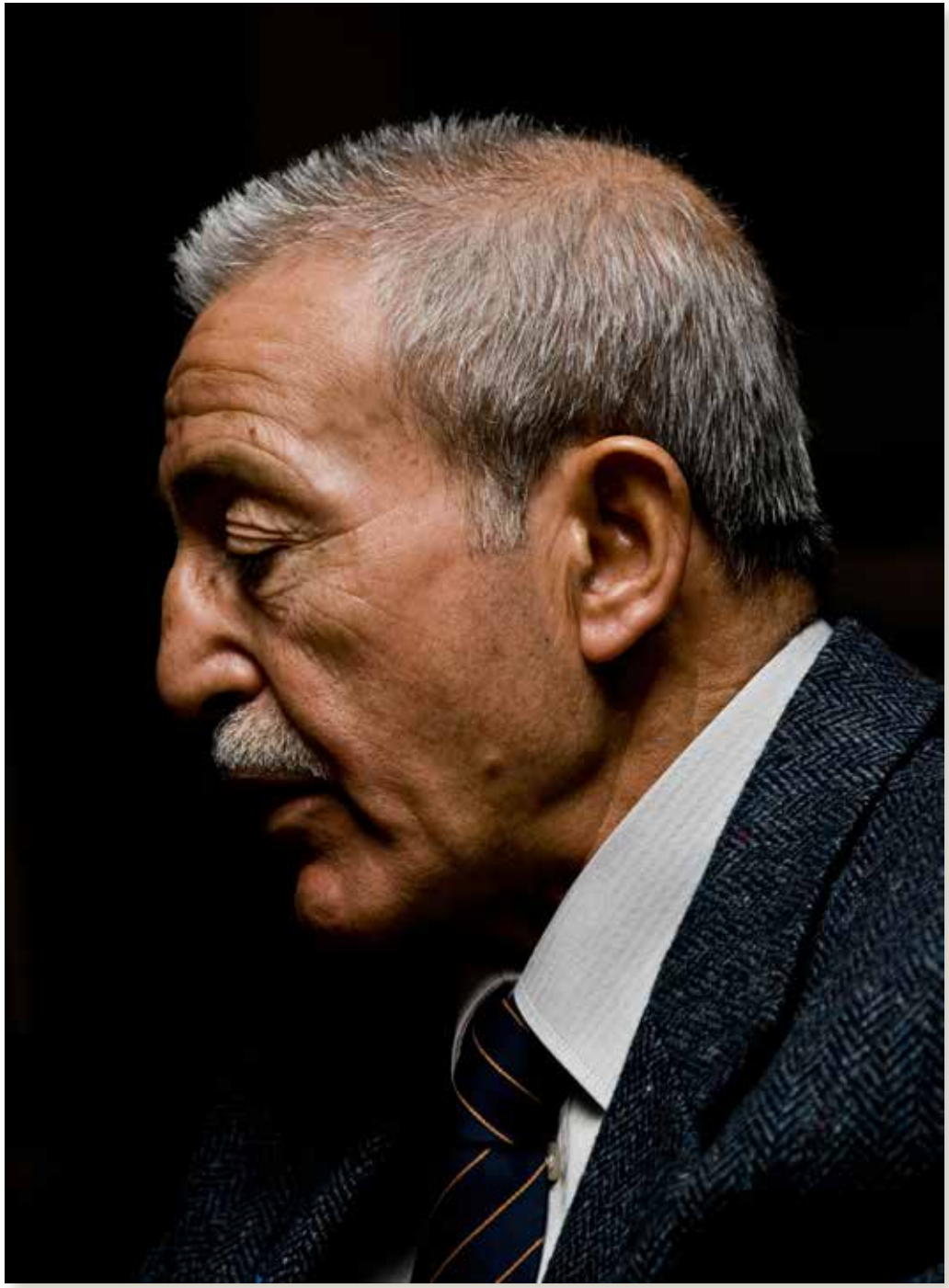
Most studies of genetic disease take place in the sterile environment of laboratories where researchers encounter patients only as bits of tissue, or as anonymous, numbered codes on test tubes and cell cultures. Fred decided to do things differently: to find the Turkish family, visit them, and enlist their direct help. In return, he could offer them medical care.

This formed the basis of a deep personal relationship between scientists and their subjects that has made all the difference. For twenty years the family has submitted to poking and prodding, welcoming foreign researchers with open arms, allowing their homes to be turned into makeshift hospitals. Several of them have been brought to Berlin – a great adventure for people who had, for the most part, never been in an airplane or traveled more than a few kilometers from their village. The story is as much theirs as that of the scientists, and this book attempts to reflect that.

Every day's headlines announce the discovery of new links between genes and disease; they rarely depict the much deeper, underlying drama of encounters between physicians, their patients, and research laboratories. Most of the stories that make the news begin in the laboratory and eventually move to the clinic. Trying to do things the other way around – starting with the patients themselves – is much, much harder. So far, it has rarely met with success.

In such cases, it is devilishly difficult to pin down even the causes of a genetic disease. Given our current state of knowledge and technology, finding a potential cure seems almost miraculous. Amazingly enough, at one point in this story it seemed to have happened. Then Fred and his colleagues faced a great ethical dilemma that has never completely left their minds.

"A potential surgical cure exists for this condition, which has not been tested in these patients," Fred says. "Could such a treatment help affected persons, and how can we be certain? We all agree that first, the molecu-



Nihat Bilginturan

lar mechanism that underlies the disease must be understood. Then we will make therapeutic assessments and recommendations."

Even without a possible cure, molecular medicine has already had a huge payoff that has been largely overlooked by the media. A clear diagnosis of a person's ailment may permit a treatment already available in the medical arsenal. That, too, has happened here – Fred's original decision to seek out the family has already saved many, many lives. Even so, his actions were the result of the journey that one of them took, long ago, to seek help.

Research into the causes of genetic diseases usually requires crossing boundaries between disciplines such as biology, chemistry, physics, and computer science – and cultural boundaries such as language, religion, and health care systems. Yet the greatest obstacle is perhaps the gap that remains between molecular biology and medicine, whose practitioners are trained in different ways, taught to think differently, and are pushed into different lifestyles. Whatever the future brings for molecular medicine, it will probably require a new generation of physician/scientist who is equally at home in both cultures. Which is why Fred Luft has devoted a great deal of his career to bringing young scientists and physicians back and forth across the boundaries.

This book is the product of dozens of hours of interviews carried out in Germany and Turkey with its major figures, including nearly all the scientists and many members of the family in Turkey. The researchers provided a rare glimpse behind the scenes of their laboratory: debates about the meaning of results and what to do next, hypotheses that led nowhere, politics, and the quirks of personalities. Most of these aspects of science never appear in a published paper. It's a bit like wandering backstage in an opera house and attending dress rehearsals before the curtain goes up on a big premiere.

In Turkey our hosts talked openly about their lives and thoughts – including discussions of religion and the problems that face their country. The family's children shared their poems, songs, and intimate dreams. "My life is so exciting I could write a whole novel about it," said one fifteen-year-old girl who goes to school in a larger town, but has never traveled more than 50 kilometers from home. I had no trouble believing her.

I have tried to recount the events as faithfully as possible, with constant assistance and comments from the figures who appear in the book. Direct witnesses have helped fill in the early parts of the story. I have made only one important change: the names and the precise location of the families who so graciously welcomed us into their lives.

The people affected by *Bilginturan's syndrome*, as the condition is now called, do not regard themselves as unusual or sick, and they should not be seen as curiosities. The discovery that their short fingers and high blood pressure are caused by a genetic defect has not stigmatized their society or made them oversensitive to differences between affected and nonaffected family members. In fact, now that their lives have been extended thanks to new drugs for treating hypertension, the disease has not shaken their lives in any major way. Except for the occasional disruptions caused by doctors and scientists whom they have come to know and trust. That could change if they were to be tracked down and made into spectacles by the media, or even if they were regarded merely as anonymous subjects in a scientific project.

Many of us who visited Northern Turkey in the context of this study have been moved by even a very short exposure to the family's way of life – a harmonious blend of nature, hard work, and religion. During the trip we had to confront and reexamine preconceptions that had

been shaped by the Western media. Very few Europeans or Americans have witnessed these societies from the inside, or heard what they have to say about the way their religion is being warped to fit political or ideological agendas. This book is not about politics or the way religion figures into world conflicts, but from time to time such themes have reared their heads, even in the course of a scientific study.

The visits to the Black Sea have been stirring personal experiences for me and every scientist who has made the trip. As a young postdoc named Philipp Maass put it, "I've spent years at a lab bench working on this kind of project in a completely abstract way. Meeting affected people and their families gives you a completely different perspective on the meaning of this type of research. The people are no longer just anonymous numbers in statistical studies, or labels on test tubes." Philipp is also a talented photographer who took many of the pictures in this book.

And then there is Okan Toka, a young doctor who grew up in Germany as the son of Turkish parents. Okan is one of the main figures of the story: Thirteen years ago, as he was looking for a thesis topic, Fred Luft convinced him to spend a year on the Black Sea to carry out a complex drug trial. The goal was to search for medications that would extend the lives of affected family members. It would be a chance for Okan to explore his roots, Fred said, and a once-in-a-lifetime experience that would be invaluable as he completed his medical training.

That prediction was more than fulfilled. Okan's adventures during his year have had a deep impact on his life. And they play a central role in this book – among other things, they inspired the title. One of Okan's patients fired an old musket, setting off a chain of events that threatened both the success of the study and the old man's life.

Since his return to Germany, Okan has spent years tirelessly collecting hypertension drugs, mostly donated by pharmaceutical companies, and getting them to the family. Few of them have medical insurance or any consistent access to medical care, so this has extended many lives.

In closure, a personal comment: It is difficult to write such a book with the distance necessary to judge the objective value of a scientific project. Many other laboratories are carrying out research into hypertension. Any of them might be the source of a breakthrough in understanding the disease. But following the story of this group captures a special moment in science, a time when our view of human health is undergoing a rapid and dramatic evolution.

We know that something is missing in molecular medicine; we still lack ideas and technologies that will allow researchers and physicians to cross the threshold from recognizing such diseases to more easily understanding their causes, treating them, and perhaps preventing them in the first place. That moment will come. It's tempting to think that the elements needed to make it happen may already be around, in some form; they may even be scattered throughout this book, like the clues to a mystery story that have so far gone unrecognized.

That has happened before in the history of science writing. *The Voyage of the Beagle*, written two decades before Charles Darwin published *The Origin of Species*, provides deep insights into the way naturalists regarded the world just before everything changed. A close reading of that work shows how all the evidence for evolution lay plainly at hand; what was missing was the powerful, integrative concept needed to draw them all together.

Only in finishing this book did I realize what is probably its central message. We live in a rapidly changing world

that has been accompanied by immense social problems. In science, this process is greatly accelerated. In the West, there has been time to integrate both types of change. Our hosts in Turkey have experienced them in a vastly accelerated form, within the space of a single generation. In this case, scientists and doctors have become important in bridging gaps of culture, technology, and health. They have done so with an unusual sense of the obligation that comes with their work – and have assumed a long-term responsibility for the family's health.

Ultimately this project – or similar ones taking place across the globe – may well lead to principles that explain hypertension and other major diseases that affect people everywhere. In the same way, the family's small hands are a symbol for something larger. You only have to take one into your own, in a clasp of friendship, to see it as a thing of beauty, an example of the wonderful diversity of our species. It is too easy to dismiss what is unusual – whether short fingers or a scarf on a woman's head – as strange and divisive, something to categorize people into "us" and "them". A deeper look reveals that such differences are to be treasured, and if we are open to them, we can learn a great deal about how to live together in a quickly changing world.

Russ Hodge, October, 2012