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All I Want for Ramadan Is My Own Mutation

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Diet, Rare Disease Day, Rare Diseases, Mediterranean, Mediterranean Food, Healthy Living News

Demoralized and despondent, I was back in my doctor's office for the umpteenth time in three years. Dr. Schorling walked in looking unsuitably chipper holding a scrap of paper torn from a note pad. So far all diagnostic roads led nowhere. The attacks of abdominal pain and fever were relentless. The pain had progressed mercilessly from excruciating to torture -- in the literal sense. Every known test had been performed on every known bodily fluid. Every body cavity had been explored (employing instruments that were conceived by our medieval ancestors for exclusively nefarious purposes) all to no avail. I could no longer envision a future for myself.

My doctor was a colleague in the Department of Medicine. He handed me the scrap of paper. Earlier in the week, in a last ditch effort, I announced a diagnosis contest -- writing up my own case history, setting all shame aside, and broadcasting it to physician colleagues and friends at home and abroad to enlist their help. That missile had been launched and now I was waiting for their responses.

"We haven't ruled this out, yet," remarked Dr. Schorling, gesturing toward the note paper. I looked down. It read, "familial Mediterranean fever." "What?" I said, "I never heard of it. You think I have this?" His answer: "Maybe" which was code for go figure it out. Then he added that he had never seen a case in his long and eventful career.

After spending hours scouring the medical literature, the answer was still maybe. I learned that familial Mediterranean fever, also known as periodic fever syndrome was an inflammatory disorder -- a deregulation of the normal inflammatory response. The symptoms were varied but often included recurrent episodes of fever and peritonitis (abdominal pain); that was me for sure. It usually starts in early childhood and most cases occur before 20 years of age; definitely not me, I was more than twice that. It is genetic; no one in my family showed signs of it. It occurs in people of Middle Eastern ethnicity including Turks, Armenians, Ashkenazy and Sephardic Jews, and Arabs: not me, at least not that I knew of. I also happened upon one inconvenient detail: this disease can kill you. Some patients produce a sticky protein, amyloid, that gloms on to your vital organs and can shut them down without warning, especially the kidneys. But no matter -- I wanted this disease. Any disease was better than not knowing what was killing me.

I met with a solid wall of skepticism at home. They didn't want it to be genetic. It wasn't exactly in their interest. They mounted counter arguments, not entirely without merit -- things I was eating, things I was exposed to, things I was doing. On balance, the arguments for and against looked about equal. At least until my friend and colleague, Susan Baker, the first to respond to my diagnosis contest, asked if she could forward my case history to a friend of hers, geneticist Victor McKusick, at Johns Hopkins for his opinion. Yes please, I responded, and the faster the better. Back came his response. In the first of several uncanny coincidences, Dr. McKusick, as if plucking the needle from the proverbial haystack on first try, recommended that I contact Dr. Daniel Kastner, at the National Institutes of Health who directs a research program

studying the genetics of... familial Mediterranean fever.

I reported back to my doctor who considered the evidence and thought it worthwhile to pursue this possibility. There was no diagnostic test but there was a treatment -- colchicine, an ancient medicinal remedy extracted from the seed of the autumn crocus. The mechanism of colchicine is very specific to FMF and alleviates the whole disparate array of symptoms including pain in many forms, abdominal pain, joint pain, rashes, fever, and amyloidosis. Because of this specificity, a positive response to colchicine is considered diagnostic for FMF. There is no equivalent alternative drug for treating FMF and since there is no cure FMF patients take colchicine for life.

FMF or not? There was only one way to find out. My doctor wrote me a prescription for colchicine, a tiny pill at 10 cents apiece. Wasting no time, I headed straight for the pharmacy and took my first dose an hour later. Thus began the first day of the rest of my life and the first step in a journey into the deep recesses of my ancestry that would take me half way around the world and lead me back home again.

The near magical resolution of the relentless cycles of incapacitating pain was stunning. Exhilaration and wonder replaced despair. I reclaimed my life as if reborn. And I soon entered into official FMF membership as a subject in Dr. Kastner's FMF study at the National Institutes of Health. Dr. Kastner is not like your family doctor. He is a research doctor -- a geneticist. I refer to him fondly as our vampire doctor who loves us for our blood. Wait. I take that back and I apologize to Dr. Kastner's lawyer. Technically speaking, it is not "our" blood since we signed away rights to the various bits when we entered the study.

I finally knew what I had which was liberating, but this instantly led to a new set of perplexing questions such as, "How the heck did I get this exotic disease?" and "If it is genetic, why doesn't anyone in my family have it?" And, "Where are these Middle Easterners I did not know I was related to and with whom I am destined to share my life-long devotion to the autumn crocus?"

I searched for an FMF gathering place on the internet and there I found my people: Yasmin, Ahmed, Lorik, Rami, Mehmet, Basem, Ghizem. Some people were connecting directly from the FMF motherlands of Egypt, Cypress, Armenia, Jordan, Israel, Turkey, Qatar. While others, like me, were from the FMF diaspora. According to scientists, the genetic trait for FMF was born in the cradle of civilization 2,500 years ago. The advances and retreats of empires, the winds of war, trade and religious conflict, had blown our ancestors from the Middle East, scattering us across many lands; Western Europe, North Africa, the Caribbean, North and South America. And here we were, despite the fragmenting forces of history, together again. There was a sense of urgency in the cross-talk, some people needed access to sources of colchicine, there were many queries about perplexing symptoms -- is it FMF or is it me? The most experienced members of the group kept watch over the fresh arrivals who needed shepherding through the bewildering first phases of treatment. Many were searching for doctors experienced in the treatment of FMF of which there is a serious shortage. But there was no shortage of helping hands in the FMF family, reaching across the cultural and historic divides; no plea went unanswered. I thought, this is a family I would choose to belong to -- if I had a choice.

But when discussion turned to genetic mutations -- one of the more popular topics -- I was out in the cold. There are about 60 known disease-producing FMF mutations identified so far but some patients still come up empty-handed in the mutation lottery -- like me. You'd think the topic would give them pause, but no, they love their mutations and no matter which ones. It fosters a lively esprit de corps. "Any M694Vs near LA? (or Cairo?)," "V726A here. U homozygous or heterozygous?" The homozygotes have it over the heterozygotes. Zerozygote -- that's what I am, with no mutation to call my own.

Who held the key to my mysterious membership in the FMF family? Did I have a Middle Eastern surprise in my ancestry -- an emir or fakir? I was seized by an urge to find out. With no clue to direct my search, I took the path of least resistance. Most of my ancestors did not leave much of a trace other than birth and death records. But there was an exception, an ancestor with an extensive historical record; might as well start with him.

Captain William Smith Young, born 1829, Port Jefferson, Long Island, was my mother's mother's father. All of his descendants know about him. It was his great misfortune that secured his place in family history. He was a steamboat captain for the Stonington line that plied the Long Island Sound, shuttling passengers from Falls River Massachusetts to Jersey City. It was touted as a luxury liner of its day. One foggy night in June 1880

his steamboat, the Narragansett, took a broadside blow from another steamboat of the Stonington line. The engine room burst into flames. Fifty souls were lost that night, all passengers of the Narragansett; Captain Young survived. It was front page news across the country. Intense coverage continued for many weeks and Captain Young was the focus of scrutiny in the follow up to the disaster. On July 17, a formal inquiry was held and Captain Young was the principal witness. His exhaustive testimony was printed verbatim in The New York Times. These were his words, and I read each one with focused attention to glean whatever insight I could of the man. And buried in this article, at the end of his testimony, was the key -- a tiny detail -- tucked away by a reporter 132 years ago, just for me.

Referring to Great Grandpa, it said, "At the opening of the afternoon session, it was reported that he had been attacked with fever and ague to which he is subject and would be unable to appear." [ague: a fever marked by paroxysms of chills, fever, and sweating that recur at regular intervals] It was him! Any medical expert would counter that malaria is a far more likely explanation for that sentence, which is true -- unless the captain's great-granddaughter has FMF -- which changes the odds considerably. With this discovery came a terrible realization that, if my interpretation of the evidence were correct, then other descendants of the captain were also at risk and it became my duty to find them.

I immediately started searching for other descendant branches of the captain and within days I found my cousin, Gail, whom I had never met. She descended from the captain's youngest son and I descended from his youngest daughter. It was a heartache to tell Gail the reason for my search -- I was hoping I was wrong. But the heartache only grew as she told me of the perplexing health problems of most descendants in her branch -- from the captain's son to his grandson to his great-grandson (her father) to her and some of her children. And there were other cousins -- lots of them with chronic health problems involving pain -- colitis, arthritis, fevers, fibromyalgia, rashes, kidney problems -- all seemingly untreatable with the standard treatments. In all, Gail and I counted about 25 descendant relatives, some from earlier generations, with a variety of signs and symptoms within the FMF spectrum, and many premature deaths.

But there was one cousin who clinched the captain's diagnosis. Cousin Kathleen, a nurse, learned about FMF during her training and she recalled thinking that she would never see a case of it in the U.S. My news finally brought clarity to the array of health issues plaguing her and her children. She reflected that she had been prescribed a brief course of colchicine for a (mis)diagnosis of pseudo-gout and it was the only time in her life that she remembered being pain free. With her spectrum of symptoms and response to colchicine, Kathleen was one cousin who met all the clinical criteria for FMF. And so, as our first common ancestor, the captain's position as FMF index case was sealed.

Cousin Gail and I immediately teamed up for some intensive genealogy research, looking at earlier generations beyond the captain for our Middle Eastern connection. We both submitted samples for a sophisticated DNA ancestry analysis, to confirm our relation to each other and to find out what ancestral population groups we had in common. Meanwhile our genealogy search revealed that the captain's parents were also born into the Long Island community about 1790. Since the captain inherited FMF from his parents, we were able to date the presence of FMF on Long Island to 1790. That finding alone was astonishing since FMF was not identified as a disease until 1945.

The DNA analysis confirmed that Gail and I are indeed related -- we were each tagged as each other's "top match." Our ancestry in both cases was overwhelmingly from the British Isles with an annoying sliver labeled "undetermined" (Neanderthal? fruit fly?). These ancestry tests are not razor sharp so questions always remain. But, so far there was still no evidence suggesting Middle Eastern ancestry.

On the genealogy front we found that once we had breached the 1790 threshold we entered a portal that led to great swaths of genealogical terrain that had been extensively mapped out by ... our relatives, it turns out -- other descendants of the same families of those Long Island communities. Following the "Young" branch of the family tree starting with Great Grandpa, we traveled back in time for six generations to the first English settlers on Long Island who established themselves in Southold. Among these first Youngs (the spelling varied over time) were Rev. John Youngs who founded the first Presbyterian church in America and his younger brother, Captain Joseph Youngs, who shuttled the first wave of settlers from Suffolk, England to Southold, Long Island and to Salem, Massachusetts in the 1640s. They were the Puritans. They fled religious persecution in England and

established strict religious communities in America that did not brook intrusion from outsiders -- not even other Christian groups. The communities were small, fertility was high and intermarriage within this society was inevitable. For those six generations between 1640 and 1790 the family trees of the founding families mixed, merged and intertwined. You could not be related to a Young if you were not related to a Tuthill or Terry or Horton or Brown (and others). "Gail" I said, pondering the expansive family tree, "We're inbred, but good."

Was FMF introduced by Middle Easterners into Puritan society on Long Island during the six generations between 1640 and 1790, or did the Puritans bring it with them? There is an abundance of historical evidence of contact between the population of the British Isles and various Mediterranean peoples during the 2,000 years preceding the Puritans' "great migration" to America (think: Roman Empire, Crusades). Conversely, we turned up no evidence suggestive of a Middle Eastern incursion into the English gene pool of the early Long Island settlers.

I am notified of another high-probability DNA match on the ancestry test. I open the publicly posted family tree of this as yet unknown person, scanning the list for familiar surnames. I get a jolt. Youngs is on the list -- and Tuthill and Terry and Horton and Brown. I click on each to see their place of birth or death. Each click yields Southold, Long Island; further evidence of my unexpected membership among Puritan descendants.

Before or after the great migration? The evidence is not all in. My own mutation might yield critical evidence about the historical pathway of my FMF ancestors and lead to other cases in my improbable cohort. Is FMF a Middle Eastern disease? About this I have something to say. This Middle Eastern disease was coursing through American society since the birth of our nation, unrecognized -- I bear witness. But genes know no boundaries and the problems we face are still the same for all branches of the FMF family -- first and foremost a lack of awareness that leaves the majority of us undiagnosed and untreated. It is a chameleon disorder that can perhaps best be described by what it isn't -- by its most common misdiagnoses, for which standard treatments usually fail. FMF can look sort of, but not exactly like: appendicitis, colitis, fibromyalgia, pseudo-gout, gouty arthritis, rheumatoid arthritis, rosacea, lupus, pancreatitis, various kidney problems, recurrent pericarditis, ankylosing spondylitis; and finally, the most reviled and unjust of misdiagnoses -- it's all in your head.

My thoughts return frequently to my great-grandfather; the scope of what he endured and the extraordinary key left behind for me -- the key meant to lead to the rescue of others. Fifty others. Fifty or more. I must do this for Captain William Smith Young that his legacy not end in the fog and the flames of the Narragansett, on that fateful night in June, 1880.

Resources:

See testimony of Captain William Smith Young, July 17, 1880
http://query.nytimes.com/mem/archive-free/pdf?res=F70C13FC3F5B1B7A93CAA8178CD85F448884F9
See Currier & Ives depiction of the Crash of the Narragansett, Museum of Fine Arts, Springfield, Mass:
http://www.springfieldmuseums.org/the_museums/fine_arts/collection//view/529-terrible_collision_between_the_steamboat_stonington_and_narragansett

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