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Discovering My Ancestral Roots and the Haplogroup Spread of BRCA1 Mutations

Corinne Renshaw
cr2350@mynsu.nova.edu

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Abstract: The purpose of this study was to trace my family lineage and incorporate my DNA test results from 23andMe to create an ancestral history. Conducting interviews with members of my family helped to relate my European ancestry to the makeup of my individual genome. Using this method, I have traced my lineage back to the mid-19th century. In doing this, I have determined my maternal haplogroup is H1c and my paternal haplogroup is probably J2. My maternal ancestor's immigration from the Netherlands and the transmission of a BRCA1 mutation are documented in this work. My paternal ancestor's immigration from Portugal and the name change from "Pereira" to "Renshaw" is also discussed. Through this research, I have written a storyline to describe who I am and why I am here today.

My family narrative begins with the start of human evolution on the plains of Africa. This was when the australopithecines developed traits that differed from those of the great apes, to be better adapted to the flood plains they now inhabited. Among these traits were bipedalism and the preference for C4 vegetation in their diet, suggesting their food source was probably tuberous roots, in sharp contrast with the fruit-eating patterns of their ape ancestors in the equatorial rainforests (Dunbar, 2016). Australopith's ape ancestors left the tropical forests because of increasing pressure for space as climate change forced densely wooded areas to recede toward the equator. Yet as humans always do, these early hominins suited themselves to their environment over time. During this time, the group of 5,000 females known as humanity's "mitochondrial eves," lived within the australopithecine communities and later gave rise to all humans today (Dunbar, 2016). These "mitochondrial eves" start the beginning of tracing human genomics and are identified by the haplogroup letter *L* (Ottoni et. Al., 2010).

Humans who branched out to the rest of the world from the original L group are identified as L1, while those who remained in Africa are identified as L0. From the L0 group, humans that migrated through the rest of Africa are known as L2 (Ottoni et. Al., 2010). The L3 group descended from L2 about 80,000 years ago and moved northward out of Africa, either across the Red Sea on the Bab-El-Mandeb or the Sinai Peninsula to reach Arabia (Ottoni et. Al., 2010). This is the group that my ancestors were a part of. Within the Arabian Peninsula, group L3 formed another group, N, which developed into many middle eastern haplogroups that we still have today.

Within group N, the R haplogroup developed and migrated from this place in search of more farmland. These new “R” haplogroups spread east and west from the Middle East over the Caucasus mountains and into Europe, developing their hunter-gatherer abilities once again (Reich, 2018). Haplogroup R overlapped with Neanderthal population’s areas, involving interbreeding and an eventual outcompeting of the Neanderthals by modern humans. As the Pleistocene Ice Age glaciers receded, certain human populations expanded further north and formed my maternal haplogroup, Hc1. Hc1 is the most common subclade in the most common clade (H1) of European lineages (Ottoni et. Al., 2010).

From their place in Europe, my mom’s family from her paternal side was concentrated in the Netherlands and made a living as flower farmers – classic Dutch! Using a family tree from my uncle Glen, who is a compulsive family ancestry researcher, I located my mother’s surname “Oosterhof” back five generations to my great, great, great grandfather, Heere Martens Oosterhoff. Heere Martens Oosterhof married Trijnte Jans de Vries and ran their tulip farm with the help of their family. The tulip business was a frenzy in Holland during the 1800s and developing one lucky variant could lead to immense prosperity. Unfortunately for my ancestors, they did not cultivate such a lucky strain. Heere Martens Oosterhof passed away by the time his eldest son, Jan Oosterhof was four years of age. When Jan was thirteen, all that remained of the Oosterhof family was him and his mother – all six of his siblings did not live past adolescence. Their tulip business had collapsed since Heere Martens Oosterhof's death, forcing the two remaining members into poverty. Jan’s mother remarried, as single women of that time often had to do. Yet Jan continually supported his mother despite her second marriage until her death on April 20, 1883. With no family to care for, Jan decided to make the world his own at the ripe age of thirty-four. Working menial labor jobs, arguably as a farm hand or factory worker, he was

able to afford the trip to America aboard the S.S. Rotterdam in June of 1884. Sitting in the hull of the S.S. Rotterdam, Jan came to America as a lowest-tier citizen. Once again, he found himself working menial labor jobs, but this time with the purpose of sending his girlfriend from home to America as well. Within the next year, he mailed her a ticket, and she soon crossed the Atlantic to find him. Through calculated plans and hand-written communication, they were able to connect in Chicago. They made their way up north to settle in the small Dutch community of Alto, Wisconsin. It is shortly after this journey that Jan Oosterhof and Trijntje Visser were married, on July 17th, 1885. The addition of a second "f" to the end of "Oosterhof" appears to have occurred at this time, though for an unknown reason.

Staying in Wisconsin, Jan eventually purchased land and began his own small farm of mostly cows, pigs, and chickens. Their four children Emma, Harry, Edward, and Tena helped to cultivate the family business further. Their first-born son, Harry Oosterhoff, born on June 24th, 1888, expanded the family farm business after his parents passed. He married Irene Van der Meer, a local Dutch community member, and they had eight children – Johnny, Clara, Kathryn, Emily, Harry, Fred, Ed, and my grandfather, Richard. After not finding much success with competing farms infringing on their profits, they decided to move to Momence, Illinois in hopes of better soil for planting crops specifically. When they moved to Illinois, they began the business Oosterhoff Gladiolas and Perennials and specialized in the farming of flowers once again as their Dutch ancestors had in the Netherlands.

Uneducated and poor, all four boys from the family were drafted into the Korean and Vietnam wars. After marching with a trumpet during the Korean War, my grandpa went back to his family in his late twenties with the incentive to settle down and manage the family farm. Being quite the ladies' man, my grandpa had many prospective suitors from the local community.

According to my grandpa, his friend Clarence wanted to ask out a lady named Marcela, but Marcela was only able to attend if her roommate went along with her. Her roommate, (and my grandma), Rita Faye Boelling obliged to accompany Marcela, so to make things less awkward for Rita, Clarence asked my grandpa to also go along. My grandpa enjoyed his time but knew Rita was already engaged to a law student at the University of Michigan and was working locally as a teacher at St. Paul's Lutheran school for only a brief time. One night at the Kankakee town square dance, he stumbled upon Rita again. They danced together for hours that night, and he decided that this time he would not assume their connection was purely circumstantial. He asked to take her on a date, which he claims was the most nerve-wracking moment of his life. Surprisingly, she agreed. The story goes that after spotting my grandma's engagement ring on her finger after having gone on a few dates, my grandpa merely asked if she would be wearing it the next time he saw her. She said no, and according to my grandpa "that was that."

Unfortunately, I was never able to meet my grandma Rita Oosterhoff. After she had conceived my mom, uncle, and aunt, she developed breast cancer twice (afflicting each breast), and later passed away from ovarian cancer. At the time, cancer's relentless pursuit of her life was an enigma. For someone to repeatedly develop the disease independently from the first tumor source was strange. The degree to which her cancer metastasized in such a short time, and occurred so early in her life, was also quite mysterious to her doctors. She only lived to be forty-nine years old, when my mom was only a freshman in college.

Looking at my grandma's family, there is a trend in the age that women develop breast and ovarian cancers. Two of her three sisters passed away from ovarian and breast cancer in their forties, indicating the possible presence of a genetic predisposition to these cancer types. In 1973, geneticist Mary-Claire King questioned why the most common forms of cancer run in

families (Duncan and Massarella, 2003). What initially spurred her interest was the fact that the most prominent factor for having breast cancer was having a mother or sister who died of the disease. By comparing similar regions of DNA from women who had developed breast or ovarian cancer, she would be able to find shared markers between them, correlating directly with the disease. To do this she sought after the Church of the Latter-day Saints genetic library, containing millions of microfilm records for Morman family research. A fierce rivalry began between her, and Mark Skolnick began when she tried to strike a deal with him to access the Morman family archives (Duncan and Massarella, 2003). He said he would only allow her access if she shared her results with him, which did not satisfy the competitive spirit of Mary-Claire King. She quickly backed out and begged families with high instances of breast and ovarian cancer to contact her via advertisements on television. She received thousands of calls, organized the families into pedigrees that indicated cancer-afflicted individuals, and took blood samples from living relatives. After working on this project for 17 years, Mary-Claire finally found a mutation on chromosome 17 that lined up with the cases she was studying (Duncan and Massarella, 2003). Pressured by James Watson into announcing this result, she communicated her findings to other geneticists and cancer specialists.

An arms race began between geneticists, to find the specific gene on chromosome 17, and within this race was King's former rival Mark Skolnick. Skolnick founded the company Myriad, which discovered the gene and was thus allowed to market and profit from the DNA test for BRCA1 (Duncan and Massarella, 2003). My mom took Myriad's BRCA1 test in 2005 when she was pregnant with my youngest brother and suffering from breast cancer. The test turned out positive for the mutated BRCA1 gene.

The BRCA1 gene functions as a tumor suppressant protein (Casaubon et. Al., 2022). Inheriting one mutated allele for this protein increases your risk for breast cancer and ovarian cancer earlier in life because the healthy allele can easily become defective through natural DNA damage, which accumulates with age. Natural DNA damage is why people without a cancer-causing mutation develop cancer, often later in life when their DNA has much wear and tear. Lifestyle factors play an important role in DNA damage, which determines how soon DNA will mutate and, as my oncologist father would say, "turn on the oncogenes while turning off the tumor suppressor genes." With a mutated BRCA1 gene, tumor-suppressant protein is already semi-functional, causing 90% of women with the mutation to develop breast cancer by the time they are seventy (Xiaoyu et. Al., 2022).

My mother shared with me her Myriad gene sequence result, and from this, I was able to estimate the geographic region and gene pool in which my mother's BRCA1 mutation originated. Her specific variant is E1134X, indicating a nonsense mutation with a premature stop codon at position 1134 of the BRCA1 protein (Pal, et. Al., 2005). Knowing that my grandmother almost certainly had BRCA1, I narrowed my investigation to German ancestry. My mom's maternal side migrated from Germany to Indiana a few generations back to practice Lutheran beliefs in the United States yet maintained relatively pure German ancestry up until my grandma married my grandpa. The inheritance of a BRCA1 mutation from the German side of my family not only tracks because of my grandma's multiple cancers but because two of her three sisters had similar experiences. Rita's sister Donna, who also went by Elsie, developed colon cancer at thirty-five and ovarian cancer at thirty-eight. She passed away at forty years old, only a year later than her diagnosis. It seemed strange that Donna would develop colon cancer before BRCA1-related cancers, so it is likely that her breast cancer went unnoticed and spread to her colon. As

breast cancer was a taboo area of oncology at the time, this was common. The cancer was often found only after it had spread outside the breast tissue. Rita's other sister Dorothy developed breast cancer at age sixty-two and passed away within that same year. Once again, this correlates with the late-stage diagnosis many women experienced at the onset of this field of medicine. Although Dorothy developed breast cancer much later, because she was younger than seventy, it is reasonable to assume she had the BRCA1 mutation. Rita's third sister, Lois, was diagnosed with colon cancer at sixty-five and passed away when she was seventy-one. Lois may not have had the BRCA1 mutation because of her long survival time, which correlates with a slower spread of the tumor, an uncharacteristic of BRCA1 tumors (Xiaoyu et. Al., 2022).

Once I laid the establishment of the BRCA1 mutations in my grandmother and her sisters, I looked for more information about my great-grandparent's health. My great-grandmother, Mary Louise Wilhelmina Brandenberg, passed away from a stroke at age sixty-five. My great-grandfather, Robert James Frederick Boelling, passed away from an infectious disease in his seventies. From this information, it appears that the BRCA1 mutation skipped a generation. This effect is usually because breast and ovarian cancers do not typically develop in men (Casaubon et. Al., 2022). So, while Robert Boelling may have carried the mutation, he never suffered the consequences of it.

Supporting the theory that it passed through Rita's paternal line is the fact that Rita's half-sister, who Mary Brandenberg conceived out of wedlock, never developed cancer of any kind. Though there is a fifty-fifty chance of inheriting the mutation from a parent, the fact that Mary Brandenberg and her daughter Mary never developed cancer makes it more likely that Robert Boelling passed on the BRCA1 mutation to his daughters. Furthermore, after analyzing my uncle Glen's family tree which extends to his great-great-great grandparents, there is a trend

in the life expectancy of females from Rita's paternal side. Robert Boelling's mother, Phonia Burke, lived to be fifty-five years old, and his grandmother, Louella Hannah, lived to be only forty.

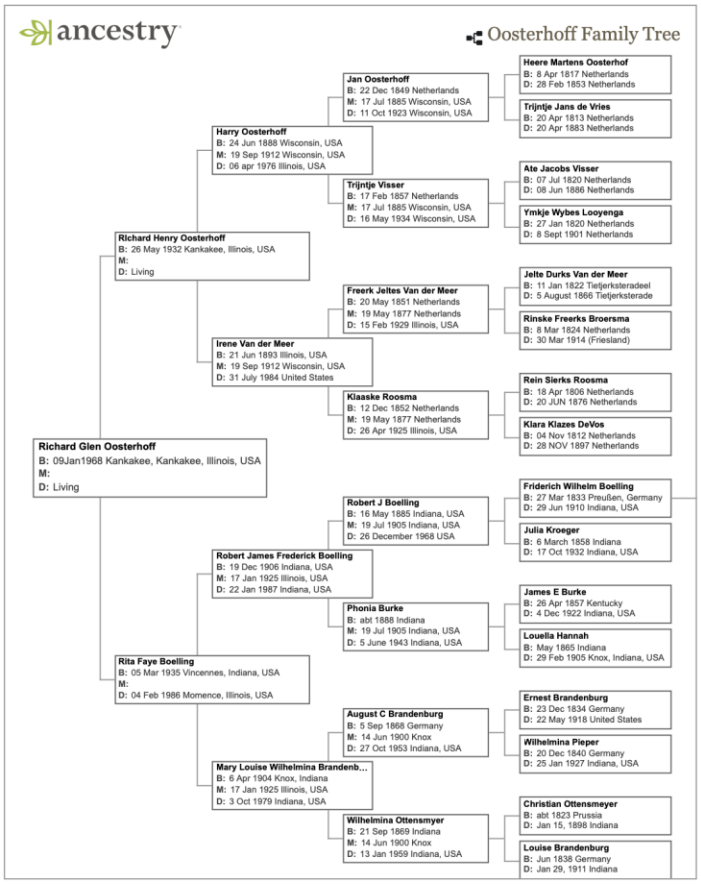

Figure 1. Maternal Line Tracing Immigration 7 Generations Back

To verify the origin of the BRCA1 variant E1134X, I researched studies that involved individuals with this same variant. One source, "*BRCA1* and *BRCA2* mutations account for a large proportion of ovarian carcinoma cases," in the *Cancer* medical journal proved that the E1134X variant came from mixed European ancestry, meaning the mutation was passed on through the founder effect (Pal, et. Al., 2005).

Table 2. Characteristics of Women who had Ovarian Carcinoma with *BRCA1* and *BRCA2* Mutations (n = 32)

Gene/mutation	Ethnicity[a]	Age at diagnosis in yrs	Histology	Stage	Prior breast cancer diagnosis with age(s)	Family history of breast and/or ovarian carcinoma
2800delAA	Mixed European	49	S	IIB	—	Yes
2800delAA	Mixed European	43	S, C	IIIC	—	Yes
3790ins[c]	British	46	S	IIIC	—	Yes
3875del[c]	English	52	S	IVC	—	No
4154delA	Mixed European	55	S	IIIC	—	Yes
E1134X	Mixed European	42	S	IIIC	41	No
K679X	Mixed European	45	E, C	IIIC	—	Yes
4440insG	Mixed European	77	S	II	—	Yes
5385insC	Mixed	52	E	IIA	50	No

S: serous; E: endometrioid; C: clear cell; PP: primary peritoneal; TC: transitional cell; U: unknown; B: Brenner cell.

a All ethnicities were non-Ashkenazi Jewish, except as indicated. b Novel mutation.

c Ovarian carcinoma cluster region.

Table 2. Characteristics of Women who had Ovarian Carcinoma with *BRCA1* and *BRCA2* Mutations (n = 32)

Gene/mutation	Ethnicity[a]	Age at diagnosis in yrs	Histology	Stage	Prior breast cancer diagnosis with age(s)	Family history of breast and/or ovarian carcinoma
BRCA1						
187delAG	Mixed European	52	S	IIIC	—	Yes
187delAG	Ashkenazi Jewish	56	E, S	IIIC	—	Yes
187delAg	Indian	43	E, S	IIIA	—	No
187delAG	Mixed European	76	S	IIIC	48, 58	Yes
187delAG	Hispanic	46	S	IIIC	—	Yes
C61G	Hungarian	56	S	IIIA	31	Yes
C944X[b]	Hispanic	54	TC	IIIC	—	Yes
1294del40	Mixed European	52	S	IA	—	Yes
2576delC	Mixed European	60	S	IIIC	49	No

S: serous; E: endometrioid; C: clear cell; PP: primary peritoneal; TC: transitional cell; U: unknown; B: Brenner cell.

a All ethnicities were non-Ashkenazi Jewish, except as indicated. b Novel mutation.

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Figures 2.1 and 2.2. Proof of Western European haplogroup relation to my mother's BRCA1 mutation, from (Pal, et. Al., 2005).

Many BRCA1 mutations that arise in haplogroups are due to the founder effect, in which reduced genetic diversity is the result of a population established by a small number of individuals. The more similar in genetic composition the population's founding individuals are, the more likely mutations are to occur in their offspring's recombinant DNA. Other populations that have a high incidence of BRCA1 founder mutations are the Ashkenazi Jewish, Arapahoe Native American, and the Dutch (Pal, et. Al., 2005). Ironically, my BRCA1 mutation did not come from the Dutch side of my family. The variants of the mutation are often congruent with the area where the founder effect originated, and these variants have different 'flavors' of the same disease. For example, the Ashkenazi Jewish variant is typically a deletion of a gene sequence region, while the variant my ancestors had is a premature stop, or nonsense mutation, along the gene sequence (Pal, et. Al., 2005). The Ashkenazi Jewish variant is also triple-negative, which means that the cancerous cells do not respond to the three main active cell sites:

progesterone binding sites, estrogen binding sites, and Her2 (or protein kinase) sites (Munster, et. Al., 2009). The variant my ancestors had is double-positive, which means that their cancer cells bound to estrogen and progesterone to enhance tumor growth (Munster, et. Al., 2009). However, this particular scenario is a catch twenty-two, because while double-positive cancers grow faster they also respond rigorously to hormonal therapy.

My mother found herself in this unfortunately fortunate scenario when she was diagnosed and treated for breast cancer. Her cancer could respond to hormonal therapy, but the holdback was her pregnancy with my brother. Blocking her production of hormones would significantly harm the health of who we now call Reuben. The doctors bombarded my mom with carefully titrated chemotherapy sessions during the pregnancy. After she gave birth to my brother Reuben, she began the hormonal therapy that would usurp her body's supply of progesterone and estrogen, the key female hormones for major female biological function. Removing her ovaries was another prophylactic measure to ensure she did not develop ovarian cancer, which has a 60% chance of developing in women with a BRCA1 mutation (Casaubon et. Al., 2022). Breast and ovarian cancer were especially correlated with my mom's variant because the hormones estrogen and progesterone regulate the ovaries and breast tissue. My mom made these decisions with the help of my dad, Gary Renshaw, a clinical oncologist by training. It is because of these difficult decisions that I can know my mom today.

My dad was born on April 21, 1958, and grew up in New Jersey all his life before attending Oral Roberts University for his undergraduate degree in biochemistry. From there, he attended the New Jersey Institute of Medicine, which is now known as Rutgers Medical School. My dad's parents were unable to afford college, so sending their son to college and graduate school was an important accomplishment for them. After graduating from medical school, my

dad did his residency at Rutgers hospital where Reuben was later born. Following his residency, he received an opportunity to work at M.D. Anderson Cancer Center within their renowned hematology and medical oncology fellowship program. This is where my dad began to specialize in oncology and decided to focus on this for the rest of his practice. While at M.D. Anderson, he became intrigued by drug development and targeted therapy approaches for cancer treatment, which coerced him into the realm of drug development rather than patient care. At the University of Michigan, he accepted a position to monitor ongoing drug trials for cancer patients there. This is where he eventually met my mom, who was working as an editor for a Christian publishing company and embarking on her Ph.D.

My mom was born on January 18, 1967, and grew up on the same family farm my grandpa did, running the "Oosterhoff Gladiolas and Perennials" business for most of her childhood. She attended Hope College, in Michigan, for her English degree. Shortly after her undergraduate years, she attended Wheaton College for her master's degree in Communications and Writing. Her goal was to be an editor and work under publishing companies, which she began to do in Michigan. During her time in Michigan, she was a member of Willow Creek, a mega-church there. Her friends knew my dad's friends through small groups and eventually set my mom and dad up together. They married on December 12, and moved to Indianapolis, Indiana for my dad's position at Eli-Lily to further work on cancer drug development. I was born in Indianapolis, Indiana on February 23, 2003.

My dad's ancestry is a bit more ambiguous, being from Ireland, Ukraine, Hungary, and Scandanavia. Due to this, the family narrative is a very complicated one that I cannot delve deeper into because I have been distant from my paternal side since my parent's divorce. Instead, I will focus on the story my father told me about my last name. The last name "Renshaw" given

to me by my paternal side is even more ambiguous than my paternal ancestry because it was completely fabricated. I must owe this to my great-great grandfather, who I also credit for my small sliver of Ashkenazi Jewish genes.

My great-great-grandfather, Louis Pereira, immigrated from Portugal in the mid-1800s. According to my dad, his paternal side of the family was displaced from Spain during the Spanish Inquisition. The Pereira's fled to Portugal where they remained for several generations. Under the increasing threat of antisemitism in Europe, Louis Pereira decided to create a clean slate for himself in America, running the Philadelphia Cigar Factory as the superintendent. In Philadelphia, he married Sarah Camp under the name Louis Renshaw. There is no record of his surname changing from Pereira to Renshaw, but the name change likely took place when he converted from Judaism to Christianity, denouncing his family's culture and religion. It is in America that he was exposed to the Christian faith and chose to adhere to its philosophy, perhaps hoping to avoid attacks of antisemitism as well. His family in Portugal held a funeral for him after his conversion, and since then the Renshaws have been cut off from their Jewish ancestors.

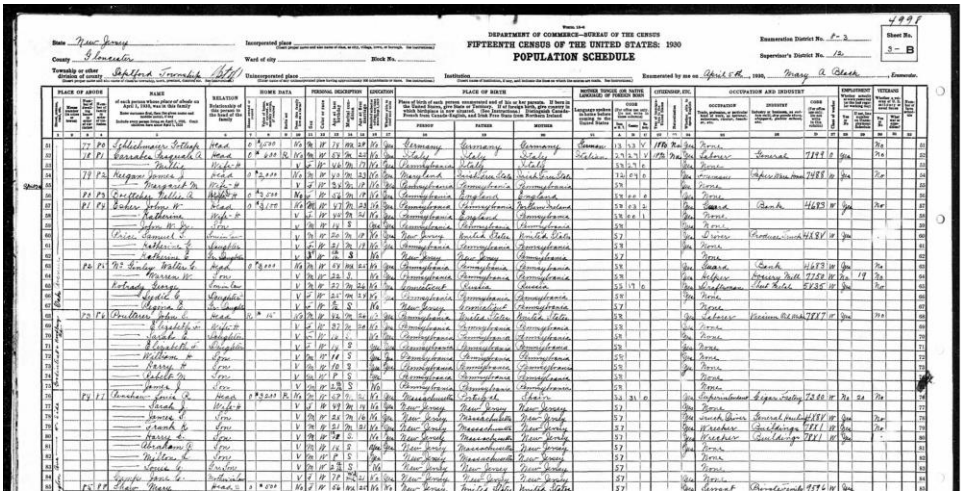
DEPARTMENT OF COMMERCE—BUREAU OF THE CENSUS
FIFTEENTH CENSUS OF THE UNITED STATES: 1930
POPULATION SCHEDULE

Figure 3. 1930's census in Philadelphia, Pennsylvania with my great-grandfather's immediate family listed

In Philadelphia, Louis and Sarah Renshaw had six sons: James, Frank, Harry, Abraham, Milton, and Louis. Their second-born son, Frank Kelly, was my great-grandfather. He worked as a freemason, according to a 1930 census, and the symbol of an eye above a pyramid on his gravestone. Freemasonry was both an occupation as well as a fraternal organization, and I suspect that many of the Renshaw business affiliations were rooted in their masonry status. My grandfather, Frank Kelly the second, was a successful businessman who sold perfumes. In the summers, however, he worked as a bricklayer for a few weeks. There is reason to suspect he was also a freemason because of this summer position. Both the surname “Renshaw” and middle name “Kelly” were passed down to me through these ancestors, giving me my name, Corinne Kelly Renshaw.

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