Myofibrillar Myopathy: A Patient's Introduction to Genetic Genealogy

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ABSTRACT

Myofibrillar Myopathy ("MFM") is an extremely rare neuromuscular disease. Most MFMs are late-onset, beginning in the fifth or sixth decade, and are characterized by severe muscle weakness, frequently accompanied with muscle atrophy, cardiomyopathy, and respiratory problems. "Myofibrillar Myopathy" as an identified disease class is fairly recent, the term being proposed in 1996.[19] The combination of being late-onset, having fairly new genetic diagnoses, and lack of awareness and knowledge among medical professionals makes it difficult to determine the history of the disease in a patient's family.

Provided here are the streamlined steps taken by the author to track a specific MFM mutation back 270 years, in a genetic pedigree spanning ten generations. In retrospect, this process required US$120, an Internet browser, and a phone, and was achieved without even leaving the house. MFM patients and those with rare genetically-identifiable diseases can replicate these steps to determine if there are affected relatives or if the mutation is new (*"de novo"*). Steps are generally applicable but are most likely to succeed with patients in the US, and those with a confirmable mutation (half of MFMs have no as-yet identified cause).

The logic and science of tracking a known rare heritable disease itself are *very* simple. It's the human element in gathering information – the fear, the unwarranted guilt, the reticence, the financial implications – that take the most understanding and the most time.

KEYWORDS Myofibrillar Myopathy; MFM

The process outlined herein is the simplest and quickest method for an MFM patient to track the inheritance of a rare MFM. If there's a family history of MFM to be found, this is the quickest way to track it.

Why?

You or a family member has Myofibrillar Myopathy or other rare neuromuscular disorder. You might not be able to climb stairs or walk across gravel or a beach. You may be in a wheelchair and have difficulties swallowing food, or you have difficulties speaking or swallowing food, or breathing. You may have a child with an NG-tube, or have one yourself. And you want to know why. Where did this come from?

You may have relatives – known or unknown – with the same disease, and it is in your and their best interests to know of each other, to gather histories, and share coping strategies. MFM is incredibly rare, and to provide a greater chance of eventual treatment, more data needs to be available.

The current MFM prognosis is, "There is no cure and no treatment." This is an unfortunate half-truth. There is currently (2020) no magic pill to cure any MFM, but there are certainly things that MFM patients should and should not do. No heavy weight-lifting. Go swimming. Daily anti-gravity exercise (walking or bicycling). No over-exertion ("If you feel what you did the next day, you overdid it. Reduce intensity and/or frequency"). Stretch twice daily, particularly the heel cords, to feel better and potentially delay the onset of contractures. Get an annual flu shot. Make sure your medical records and emergency card include your diagnosis, specifically because of life-threatening problems with some general anesthesia (some

could severely damage muscle, and you may not be able to resume breathing unassisted after coming out of anesthesia). Don't buy a two-story house and expect to climb the stairs later in life. Get supplemental insurance. Don't wait until you're retired to take your dream vacation, unless your dream vacation includes crutches or a wheelchair. Even it there is currently no cure for an MFM, it is still worthwhile knowing which actions to take or avoid.

Actual steps

Conceptually, this starts with gathering information from those relatives closest to you (siblings, parents, aunt and uncles, and first cousins). If you can determine that descendants of a set of grandparents have the same symptoms or confirmed mutation, attempt to determine which grandparent it was. If known, expand your search to that grandparent's siblings and first cousins. If you can't determine which grandparent it may have come from, search both grandparents' siblings and first cousins.

At every step the mutation is either inherited or is a *de novo* mutation. The goal is always to identify if the disease was inherited from the father, or from the mother. Once that has been determined, repeat the process.

Ancestry.com's "Thrulines" makes this *ridiculously* simple. Note that autosomal DNA can't let you know precisely how you're related to someone, the farther back you go; someone sharing 3% of your DNA could be either a second cousin, or a first cousin twice removed. But for the purposes of tracing a rare inherited disease, it doesn't immediately matter – you'd ask them for information either way, and sort out the details later if there's a promising response.

With an autosomal dominant disease, each child has a 50% chance of inheriting the disease. If you find an affected woman who had eleven children, and the woman was one of ten children, there should be a quite a few MFM descendants from her parents.

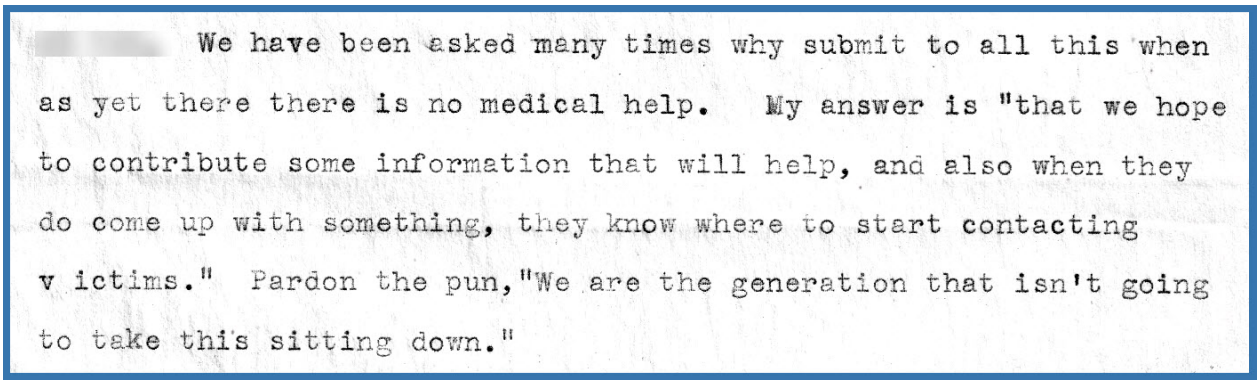
These steps assume familiarity with Ancestry.com or willingness to acquire the basic skills; there are a lot of videos and tutorials, and it's not difficult after the first few hours of acquaintance. Other genealogy services like myheritage.com are useful the more involved in a search, but Ancestry.com is by far the simplest and most productive genealogy site to start with.

Exercise discretion; most people are very private about family medical history.

Follow in this exact order to minimize overall time and maximize results. Check off any step you may have already completed, as this process assumes you're starting from scratch.

- Ancestry.com preliminary work. The optimal method requires getting an autosomal DNA test from Ancestry.com, which will take about a week to get sent to you, for you to take the test, send back the results, for them to get it, and then about a month before results are available for you to search DNA Matches and use Thrulines. During that 5-6 weeks until you can start searching for DNA matches, there are things that are either prerequisites or can be done in parallel.
  - ☐ Create your free Ancestry.com account.
  - ☐ Order an Ancestry.com autosomal DNA kit for the affected person (likely, you).
  - ☐ Optional: order an additional DNA test for affected relatives higher in family tree, if known and they are amenable. Autosomal DNA test usefulness deteriorates with each generation, and as a practical matter, Ancestry.com will only show possibilities of common ancestors up to five generations. If it's possible your MFM history exceeds that, then using the DNA results of people higher in the genetic tree should help you match farther back, and wider.
  - ☐ Ancestry.com: fill out your family tree, covering the highest known-affected person[s], plus *at least* two generations (their grandparents).
  - ☐ Produce your introduction to relatives. You'll send this message to relatives, personalizing and customizing for each recipient. Example template:

    > Dear distant cousin,
    >
    > <include your name and how you're related [if known], or at least how you decided to contact them (DNA match, family tree, etc)>
    >
    > Some descendants of at least John and Jane Doe have a history of a very rare form of late-onset muscle disease, and a few of us are trying to track this back as far and wide as we can and let others who may be affected know what to look out for. There are some very specific problems we have, and it would be beneficial to compare notes to be able to provide more information for ourselves, our doctors, and caregivers.
    >
    > SYMPTOMS: Usually in the mid-40's, we start developing walking problems due to weakness in the legs, especially noticed when climbing stairs. This is followed by foot-drop, where the toes droop when walking, and we lift our knees high so our toes can clear the ground ("steppage gait"). This is followed with stumbling, tripping, and falls, eventually leading to using a cane/crutches/walker, and is usually followed by wheelchair confinement.



We have been asked many times why submit to all this when as yet there there is no medical help. My answer is "that we hope to contribute some information that will help, and also when they do come up with something, they know where to start contacting v ictims." Pardon the pun,"We are the generation that isn't going to take this sitting down."

Figure 1 Excerpt from a 1979 letter, from a woman explaining why she, her daughter, her brother, and her first cousin had muscle biopsies.

It should be very noticeable if there's a family history of this (you've attended a family reunion that looks like a walker and wheelchair convention).

Do you know of such a history in your branch of the family?

Thanks! Your Name

☐ Produce your introduction template for family tree maintainers, relatives who already have family trees built that cover the area of your family you're investigating. They universally *love* genealogy, and it is *vital* to get acquainted with them. Base your introduction on the generic relative introduction above, and also explain that you're attempting to track your family history of the muscle disease (don't say "MFM") and that you're grateful for the genealogy work they've done. *Especially* ask along the lines of, "Have you had anyone else contact you about a similar disease? If so, can you send me their contact details so I can get in touch? Or at least send them my contact details and let them know I'd very much like to talk to them?" Do not skip asking this question.

☐ Introduce yourself to any tree maintainers who seem to know a lot about your near relatives. If your grandfather had MFM, and there are second, third, or fourth cousins who have him in their family tree, send your introduction to them. Personalize it a bit, notably if you know how you're related already. These people will also likely have posted on familysearch.org, wikitree.com, or other similar genealogy sites. Note that some family tree maintainers have 20,000-people family trees, where they'll just basically copy and paste from anyone's tree; they're unlikely to be of any help.

☐ Optional: pay for database access. Some Ancestry.com databases are free, including the 500 million free documents served in partnership with the US National Archives and Records Administration (NARA), but when expanding your search, the paid specialized databases (for example, christening records from 1810 Prussia) have proven invaluable. Death and marriage certificate searches alone were worth the subscription.

- Self-education
  - ☐ Acquire the most recent edition of "The Family Tree Guide to DNA Testing and Genetic Genealogy."[5] This is a very inexpensive, accessible, and informative book.
  - ☐ Determine how you'll organize your investigation. Buy an acid-free paper sketchbook or notebook, and/or begin your your digital collection (e.g., EndNote).
  - ☐ Download the PDF of "Help Me Understand Genetics."[12] This is a comprehensive primer from the US National Institutes of Health.
  - ☐ Download the PDF of the "Standardized Human Pedigree Nomenclature..."[4] Figures 1 and 2 provide simple explanations of plotting a genetic pedigree – a family tree based solely on DNA and inheritance. There are numerous online pedigree tutorial videos, like "Genetic Pedigrees (by Beverly Biology)." Sketching out quick pedigrees while talking to relatives is a good skill to acquire. Become familiar with reading and drawing pedigree charts; it's fairly simple, and the basics boil down to: "Square box" means "male." "Circle" means "female." "Diagonal line through" means "deceased." "Filled in" means "affected." The layout shows generations and marriages (or, "mating events"). The remaining details are largely specialized esoterica not germane to this task.
- Ancestry.com – after DNA results available

- ☐ Link your Ancestry.com DNA results to your family tree. (Optional) If other affected family members have Ancestry.com DNA results and are amenable, work with them to link their DNA test to your family tree. See Ancestry.com's online help for instructions.
- ☐ Wait a day while Ancestry.com's background processes determine your DNA matches and build relationship guesses in ThruLines. Once this is done, the process really speeds up.
- ☐ When your DNA Matches and Thrulines are populated, start making contact. For the highest-known affected family member, contact descendants of a generation higher, to start with. For example, if your maternal grandfather is the highest person you know of with MFM, contact DNA matches for his descendants (aunts, uncles, and first cousins, and lower), his siblings and their descendants (second cousins), and one level higher to his parents' siblings and descendants.
- ☐ It's tempting to contact all DNA Matches in one fell swoop, but that's generally considered bad etiquette, even with something as important as searching for a rare disease. The real problem with untargeted contacts is that you'll introduce a lot of false positives, and you'll also introduce false negatives (see the "Talking to Relatives" section later). Assuming no cousin marriages, each person has *eight* great-grandparents. Replies from descendants of *six* of those eight will be completely meaningless to you, so don't invite needless noise. Limit initial inquiries to only those that are close to the highest-known affected relative. At each step, divide and conquer, and reduce the search space — family trees get very large, very quickly. See https://isogg.org/wiki/Cousin_statistics and https://isogg.org/wiki/Autosomal_DNA_statistics to see how unwieldy mass requests can become. For example, the average British person has 174,000 living sixth cousins, and there is only a 2-11% chance of a genetic match to a given sixth cousin.
- ☐ Remember why you're doing this. There is a rare muscle disease, and you want to help yourself and your relatives with the same affliction. You're trying to find them all.

Sample Walkthrough

See figures 3, 4, and 5 for a sample walk-through of four generations of a woman with a confirmed autosomal dominant MFM mutation. To keep it simple, there are no consanguineous marriages, and deaths are not marked.

The goal is always the same: for the highest known-affected, try to determine which parent it came from. With each iteration, working higher, the MFM was either inherited from a parent (rarely both), or it is a *de novo* mutation.

Each child of an affected patient has a 50% chance of inheriting the disease.

Contact the question marks.

Challenges

Myofibrillar Myopathy is a relatively new classification

"Myofibrillar Myopathy" is a term first proposed in 1996. No family medical records before then will ever mention this term. Even now (2020), most doctors know nothing of MFM.

Understand the inheritance pattern

If the mutation is known, and the inheritance pattern has been established (e.g., autosomal dominant), then you can tailor your investigation to a smaller set of possible ancestors.

If the inheritance pattern is unknown (i.e., it might be recessive), you'll have to start your initial search an extra generation higher than otherwise. That is, start your initial search three generations higher than the highest-known affected relative.

Review the "Help Me Understand Genetics" primer. Search for and watch online videos about "DNA inheritance."

Of the *known* MFM genes, four-and-a-half LIM domain protein 1 (FHL1) is the only one on the X chromosome[18]. Other MFMs are all autosomal, overwhelmingly with dominant inheritance, though a very small percentage of MFMs are recessive, like $MYOT^{R6G}$.[17]

Chromosome locations: DES (2q35), CYRAB (11q23.1), MYOT (5q31.2), LDB3 (10q23.2), FLNC (7q32.1), BAG3 (10q26.11), KY (3q22.2), PYROXD1 (12p12.1), TTN (2q31.2), FHL1 (Xq26.3 – X-linked), PLEC (8q24.3), LMNA (1q22), ACTA1 (1q42.13), HSPB8 (12q24.23), SQSTM (5q35.3), TIA1 (2p13.3).

De Novo Mutations

All mutations start somewhere, by definition. A "*de novo*" mutation is just that – a change "anew." It's a mutation that neither the father or mother show; the mutation occured in either sperm, egg, or during early embryonic cell division.

If an MFM patient with a confirmed mutation has no known family history of muscle disease, the obvious next step is to test the biological father and mother, if available. If father and mother both test negative, then the mutation is *de novo*, not inherited, and there is no further family

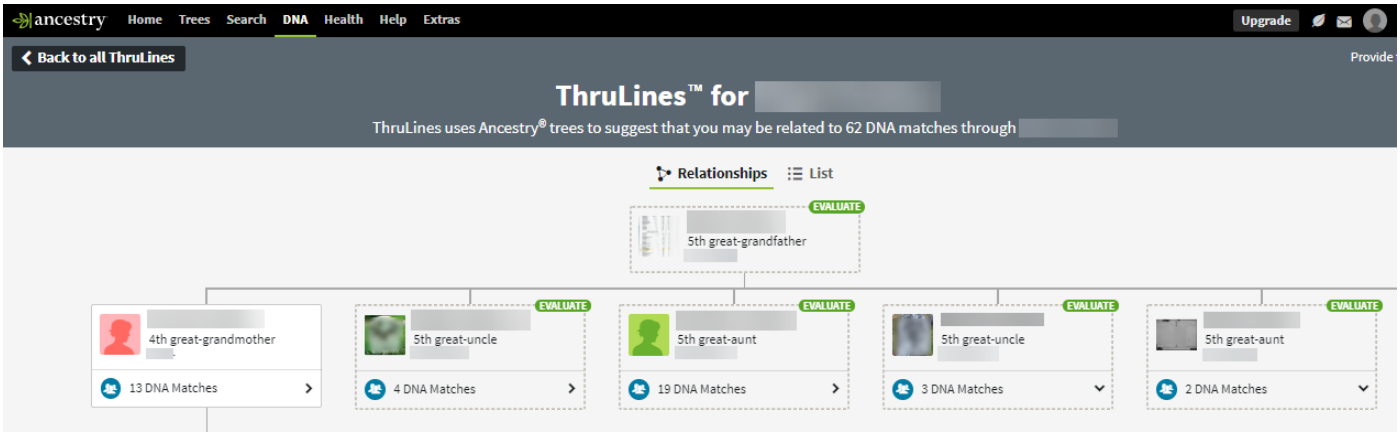


Figure 2 Ancestry.com's ThruLines™ feature is easily the biggest time-saver in this endeavor. After attaching your DNA results to your family tree, you can view DNA Matches in a best-effort family tree (if any exist, of course). Expand the lines you're interested in, select the relatives you'd like to contact, and then compose a message to them. MyHeritage.com has a similar feature, and some other genealogy sites have some rudimentary capability, but Ancestry.com's is by far the simplest to use and has more participants [in the USA]. There are more extensive methods that require advanced know-how (e.g., DNA Painter, GEDMatch, etc.), but for quick and easy results, use ThruLines.

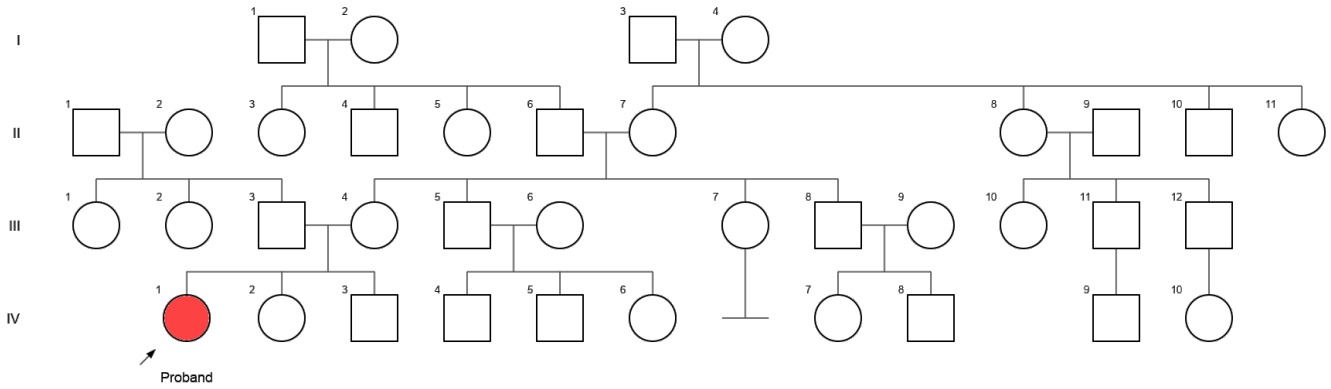


Figure 3 The "proband" here is an MFM-affected woman [IV.1], filled in red. She has a sister [IV.2] and a brother [IV.3]. Either her father [III.3] or mother [III.4] were affected, or it was a *de novo* mutation (neither parent had it).

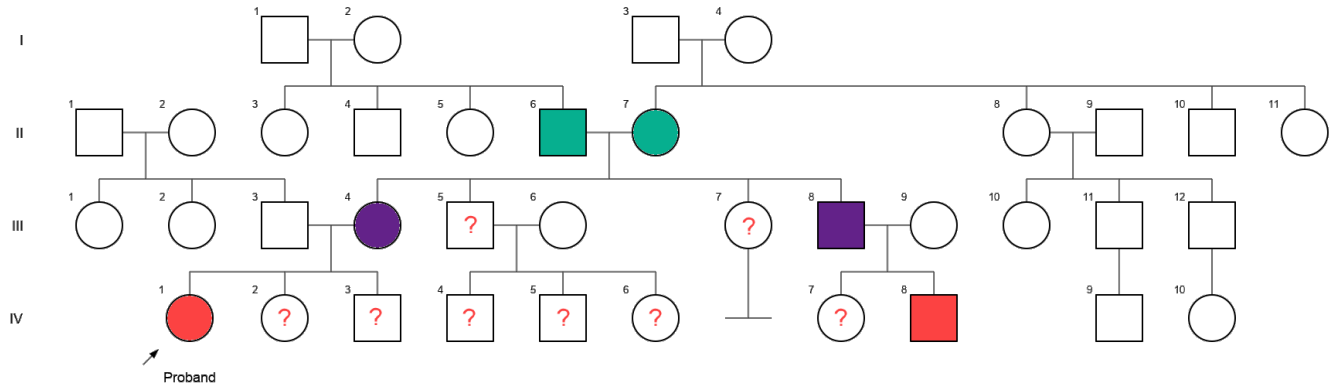


Figure 4 Assume the affected woman knows nothing else than that her first cousin [IV.8] has the exact same incredibly rare MFM mutation (also filled red). It is unreasonable to assume they independently had the same rare *de novo* mutation, so follow the inheritance to the Most Recent Common Ancestor (MRCA). This would imply that the woman's mother [III.4] and her maternal uncle [III.8] (both filled in purple) were affected, and that they inherited it from, or it was *de novo* with, either grandparent [II.6] or [II.7] (filled in green). Since each child of an affected parent has a 50% chance of inheritance, the relatives marked with question marks have a possibility of inheriting it.

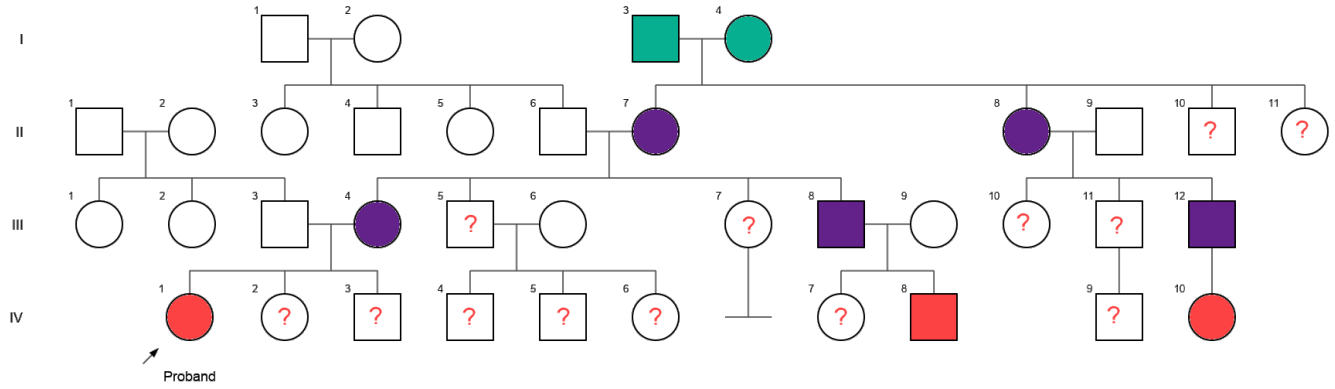


Figure 5 Keep iterating. The woman discovers a second cousin [IV.10] with the same very rare MFM mutation, which was therefore inherited from great-grandparent [I.3] or [I.4].

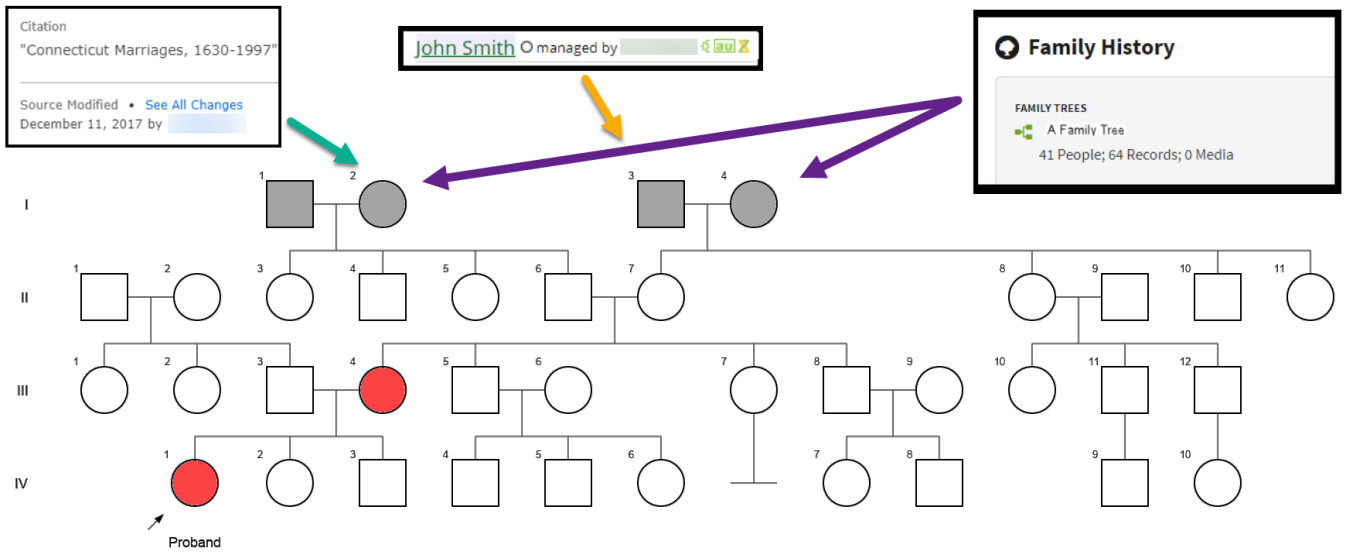


Figure 6 *Ask for help.* Genealogy sites include Ancestry.com, WikiTree, FamilySearch, MyHeritage, and others. Introduce yourself to any family genealogists who seem to have knowledge of the branch of the family you're investigating. Ask if they know of any history of any muscle disease in the family. Ask if anyone else has asked them this question, and if so, ask how to make contact. From the highest generation you know of [III.4 here], ask about a couple generations higher (filled in gray here). Search for obituaries, death certificates, or any other indication of the presence of a muscle disease.

history to pursue.

See the paper "New Insights into the Generation and Role of *De Novo* Mutations in Health and Disease,"[1] especially the section "Parental Origin of *De Novo* Germline Mutations." Among many interesting points: "Approximately 80% of all *de novo* germline point mutations arise on the paternal allele, and advanced paternal age at conception has been established as the major factor linked to the increase in the number of *de novo* mutations in the offspring, both at the population level and within the same family."[1]

Early-onset MFMs are more severe and more likely to be *de novo*, since problems are generally known before the MFM patient gets to the age of procreation. For example, "[t]he severity of classical BAG3 myopathy is illustrated by the fact that the p.P209L mutation has been found to be *de novo* in all but two reported cases."[16]

Inherited MFMs, on the other hand, tend to be late-onset; a patient could have grandchildren before displaying any muscle problems.

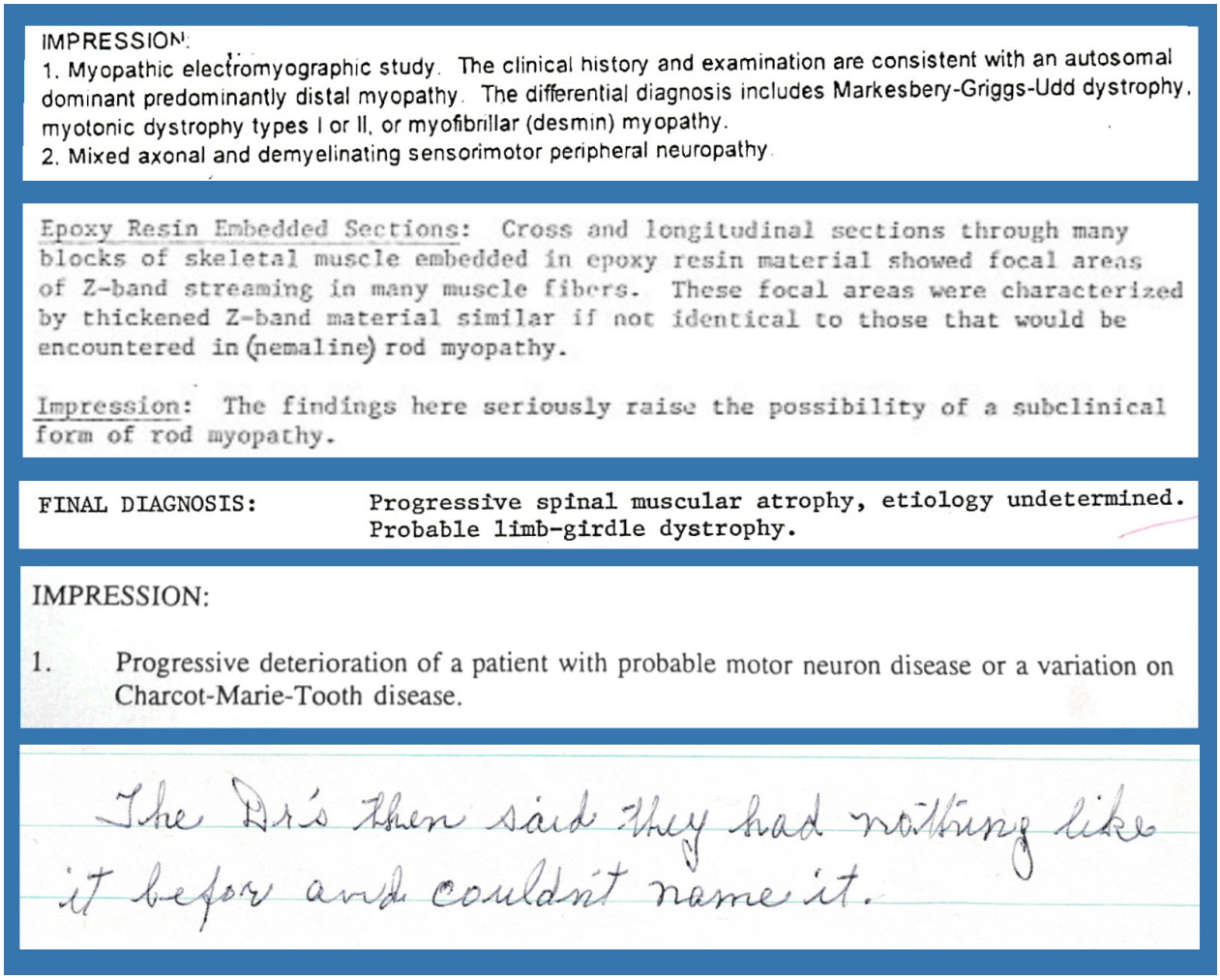
Family Histories

In the United States, at least, it's very rare to keep track of anyone beyond grandparents and first cousins. Some people simply don't care to know anything about their family history. If an affected parent or grandparent dies before showing any symptoms, or if the parents are estranged, an MFM patient would share in no collective memory of a disease that might span generations. It's not terribly uncommon at all now for people to know little if anything about one side of their family. Adopted children likely know nothing at all about either parent. It is not unheard of in human history for someone to not know that their father is not really their biological father, or more rarely, that their mother isn't biological mother.

If a family history is known, that will be shared with a doctor or neuromuscular clinic, but it's not immediately evident when families are connected. Surnames change quite frequently, most frequently when a wife adopts her husband's name. When a DNA test is run to diagnose a suspected MFM and a mutation is identified, there are no additional genealogy-type tests for near relationships to others with the same mutation.

Two MFM patients with an identified mutation see the same doctor at a leading neuromuscular clinic. Their known [to them] families don't have the same people or even the same surnames. They provided DNA samples, but no one compares the DNA to see if they're related – the goal is to identify or confirm the mutation, and it's assumed that they represent separate founders. But they are actually third cousins once removed, having inherited the disease from the same person, and each has no idea the other exists (real-life example).

It is *incredibly* important to gather as much family medical history as soon as you can. Documents get lost. People don't live forever, and memory may decline, so talk to relatives as soon as possible. Don't delay. Two lines in an old letter can make a tremendous difference.



IMPRESSION:
1. Myopathic electromyographic study. The clinical history and examination are consistent with an autosomal dominant predominantly distal myopathy. The differential diagnosis includes Markesbery-Griggs-Udd dystrophy, myotonic dystrophy types I or II, or myofibrillar (desmin) myopathy.
2. Mixed axonal and demyelinating sensorimotor peripheral neuropathy.

Epoxy Resin Embedded Sections: Cross and longitudinal sections through many blocks of skeletal muscle embedded in epoxy resin material showed focal areas of Z-band streaming in many muscle fibers. These focal areas were characterized by thickened Z-band material similar if not identical to those that would be encountered in (nemaline) rod myopathy.

Impression: The findings here seriously raise the possibility of a subclinical form of rod myopathy.

FINAL DIAGNOSIS: Progressive spinal muscular atrophy, etiology undetermined. Probable limb-girdle dystrophy.

IMPRESSION:

1. Progressive deterioration of a patient with probable motor neuron disease or a variation on Charcot-Marie-Tooth disease.

The Dr's then said they had nothing like it before and couldn't name it.

Figure 7 MFM is a relatively new diagnosis. Parents and grandparents had the best diagnoses based on the medical knowledge of the time. Here are four diagnoses of what turned out to be the same MFM mutation. A family letter recounts a visit with neurologists at the Mayo Clinic in 1956: "The Dr's then said they had nothing like it before and couldn't name it."

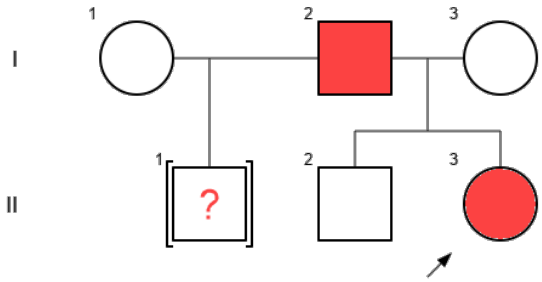


Figure 8 [II.3] knows of a half-brother who was adopted out [II.1]. Since they share a common affected father, the half-brother has a 50% chance of inheriting the MFM. It is overwhelmingly probable that the half-brother has no idea there's a family history of a rare muscle disease. [II.3] could take an autosomal DNA test with Ancestry.com and/or 23andMe to make it easier for the half-brother to make contact and discover his origins.

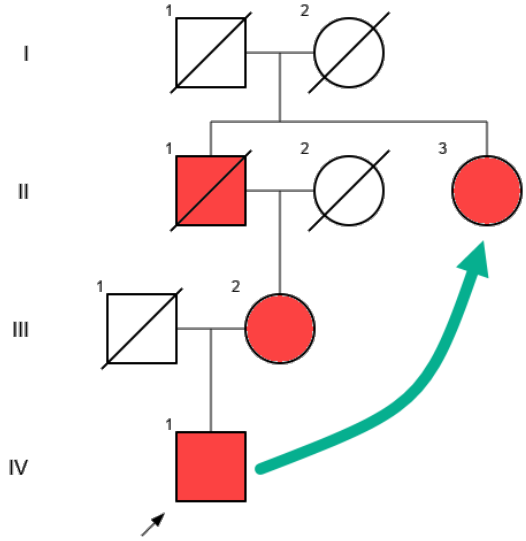


Figure 9 [IV.1] has taken an autosomal DNA test for genealogy. He should ask his great-aunt [II.3] if she's amenable to doing the same and allowing him to search Ancestry.com using her DNA results. This automatically covers two generations higher. It doesn't matter if she's affected, if there's no question of parentage.

Lost to history

All genealogy research is subject to eventual defeat by knowledge lost to the mists of time; perfect record haven't been kept and maintained back until the beginning of human history. There will be so-called "brick walls," places you're currently, and possibly permanently, unable to find any additional information. Standard genealogy strategies apply; search the Internet for pointers on "genealogy brick walls."

Late-onset vagaries

Most Myofibrillar Myopathies are late-onset: symptoms aren't apparent until the 5th or 6th decade of life, with some variation either side of that. The farther back genealogies go, the shorter the lifespans in general — if a woman died at 50 a couple hundred years ago, she may not have started exhibiting symptoms yet, and it's exceedingly unlikely that there would be written records even if she did.

Determining medical history is, of course, much more difficult than determining ancestry in the first place. If an ancestor died at 40 from pneumonia, this tells little about his possibility of MFM.

Odds

There's an adage among doctors: "When you hear hoofbeats look for horses not zebras." That is, don't lean toward a diagnosis of some rare and exotic disease when a common malady is far more likely.

But what if you live on a zebra farm? What if the patient has a known recent ancestor with a heritable MFM?

A contrived, extreme example for illustration:

RARE disease has a 1 in 1,000 frequency among the *general random* population. One in a thousand.

SUPER-RARE disease (autosomal dominant) has a 1 in 1,000,000 frequency among the *general random* population. One in a million.

Assume RARE and SUPER-RARE present the same symptoms, so, *given no other information*, a patient would be one thousand times more likely to have RARE than SUPER-RARE. Doctors are familiar with RARE but don't know so much – if anything – about SUPER-RARE and have probably never seen a single patient with it. The doctor will tend toward RARE and not SUPER-RARE.

But "general random population" is *not* the same as "family population with a known autosomal-dominant ancestor."

One of Jane's parents had SUPER-RARE. Jane's odds of having SUPER-RARE are one in *two* (50%), not one in a million (0.0001%). Jane's odds of SUPER-RARE given an affected grandparent: 25%. Having an affected great-grandparent: 12.5%. 2x-great-grandparent: 6.25%.

If nothing else is known except that one of Jane's great-great-grandparents had SUPER-RARE, Jane's odds of having SUPER-RARE are actually *62.5 times* greater than having RARE.

Another example (See figure 10): assume for the sake of illustration that Myofibrillar Myopathy and Charcot-Marie-Tooth have the exact same frequency in the general population (CMT is actually more common). MFM patients in the past (earlier than the year 2005, say) have sometimes been diagnosed with CMT, as genetic diagnosis was unavailable, and the symptoms are close.

A distant cluster of symptomatic siblings say they have Charcot-Marie-Tooth, because that's what their father was diagnosed with in 1995, but they and their father have never had a DNA-test confirmation. The frequency of CMT worldwide is estimated at 1 in 3300.

You know for certain that their father's grandmother had an autosomal dominant MFM, so their father had a 1 in 4 chance of inheriting the MFM, regardless of MFM's general frequency.

Absent any modern diagnostic confirmation, with MFM and CMT presenting similarly, it is *825 times* more likely their father had MFM than CMT. It's entirely possible their father had CMT (it's a cruel and unforgiving universe, and strange things happen), but they shouldn't be precluded from gathering more information and would be noted as very highly likely MFM, followed up with a gentle and humble suggestion that DNA confirmation might be in order, to make sure they're treating the correct disease.

Another example: suppose a woman in the mid-90's (before MFM was recognized) was diagnosed with Inclusion Body Myositis (IBM), but it is known that her grandmother had an autosomal dominant MFM. IBM and MFM present similarly, and known MFM patients are known to have previously been diagnosed with IBM. The estimated frequency of IBM in the USA is seventy per million – 1 in 14,285. A grandchild has a one in four chance of inheriting an autosomal dominant disease. 14285/4 = 3571. It is over 3500 times more likely that the woman had MFM than IBM.

A final example that illustrates the logic behind triangulating transmission paths: Bob and John each have an autosomal dominant mutation that has only twenty documented instances. Not every case is going to be documented, so assume there is actually a full fifty times that: a thousand people in the world with their specific mutation. The current (2020) world population is 7.8 billion; one out of 7.8 million people have Bob's and John's mutation. Bob and John are first cousins (their mothers are sisters). What are the odds that Bob and John each separately have a *de novo* mutation of the exact same incredibly rare mutation, vs. the odds they inherited the mutation from a common ancestor (one of their maternal grandparents)? It's negligible. Stacy has the same rare mutation. She is Bob's and John's second cousin. There's virtually *zero* chance they all three spontaneously developed the same incredibly rare mutation – it just didn't happen. Bob, John, and Stacy inherited the mutation from a common ancestor.

Silver Lining

The silver lining to the rare disease cloud is that it's much easier to determine or rule out inheritance paths. Plotting a definitive pedigree of diseases like cancer or diabetes would be impossible; they're just too common and indeterminate. Finding first, second, or third cousins with the same one-in-a-million mutation makes the genetic genealogy a lead pipe cinch.

Consanguineous Marriages

Consanguineous marriages are marriages between second cousins or closer, colloquially known as 'inbreeding.' Approximately 10% of the current global population is a member or product of a consanguineous marriage[6], and there are numerous historical and social reasons for such marriages, such as retaining property within a family. The farther back an MFM pedigree reaches, the more likely it is that consanguineous marriages are encountered.

Close marriages are commonly known to increase the incidence of serious disease, since recessive diseases tend to be more severe than dominant diseases, and close marriages greatly increase the odds of inheriting two copies ('homozygous') of the mutation.

In an autosomal dominant disease, with both parents being affected, on average:

- **50%** of offspring would be heterozygous for the mutation (have one copy of mutant gene, and one normal copy). This is the 'normal' state of the disease.
- **25%** of offspring would be homozygous for the mutation (both copies of gene are mutant), and the disease would tend to be much worse, with earlier onset and much more severe symptoms. For example, "The unusual congenital presentation of the disease clearly demonstrates that homozygosity for mutations in FLNC [$FLNC^{P442R}$] severely aggravate the phenotype."[11]
- **25%** of offspring would be unaffected (both genes are normal).

Compare to the more usual autosomal dominant case when only one parent is affected, where on average: 50% of their children are affected, and 50% are unaffected.

Consanguineous marriages do have one beneficial side-effect when tracing rare diseases: much more genetic material is retained, so DNA match searches can go back farther. Normal autosomal DNA tests become untrustworthy after five generations; DNA matches for consanguineous offspring can go farther than five generations.

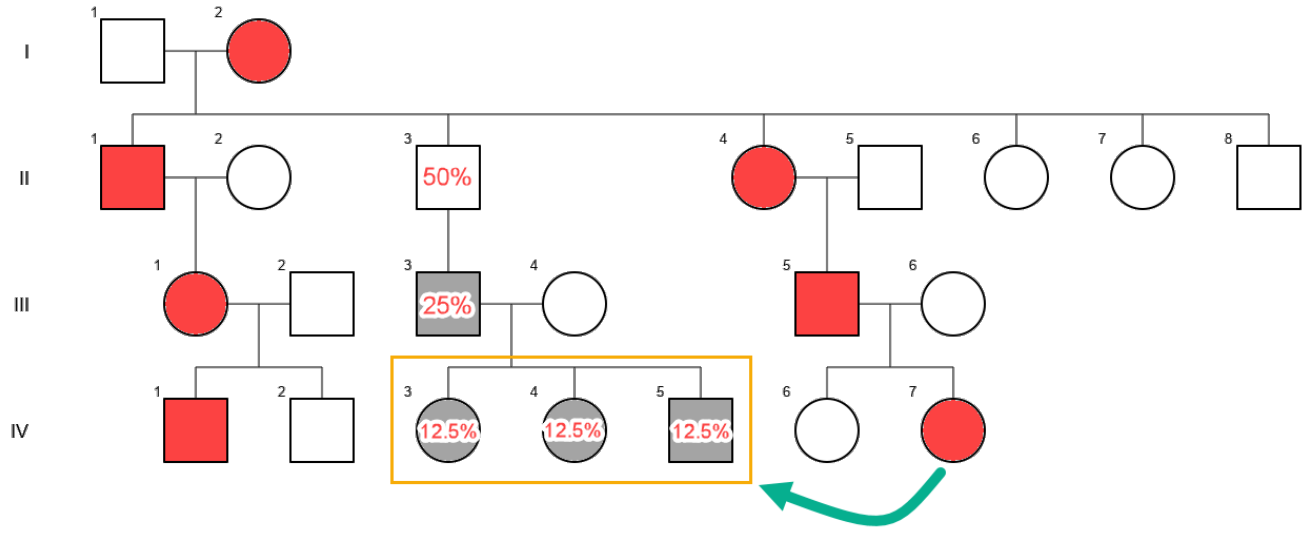


Figure 10 [IV.7] is investigating her family history. Her second cousins [IV.3], [IV.4], and [IV.5] – unknown to her yet – all have a late-onset muscle disorder whose symptoms match her MFM. Their father [III.3] had the same issues and was diagnosed in 1995 with Charcot-Marie-Tooth ("CMT"), with no DNA confirmation. None of the second cousins have had DNA confirmation of CMT. They "know" they have CMT because that's what their father was diagnosed with, twenty-five years ago. If [IV.7] sends an initial inquiry, mentioning a specific MFM mutation, it's very likely to be ignored by her second cousins, because they don't know what "MFM" is, and they think they have another disease entirely. *Always* keep initial questions and conversations generic and focused only on the symptoms; narrow down specifics later. Absent negative or positive genetic confirmation of their father and grandfather, they have a 12.5% chance of having MFM, which is far higher odds than independently having CMT. It would be prudent to share the family history with them, and suggest they have DNA testing for the MFM and CMT, to make sure they're treating the correct disease.

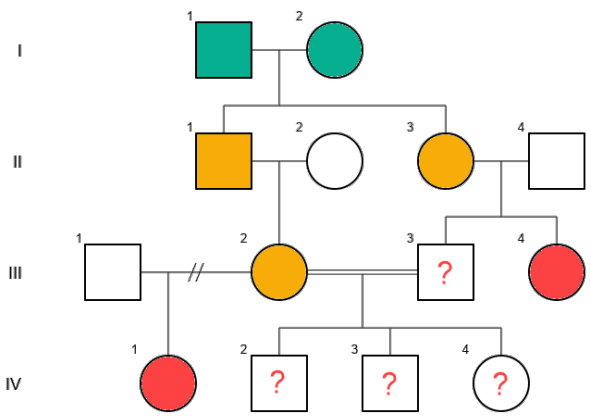


Figure 11 Example of consanguineous marriage (red = known affected, orange = implied, green = possible, and question marks = possible affected). [III.2] and [III.3] are first cousins. It's possible [III.3] was affected, but is unknown here. If [III.3] was affected with an autosomal dominant disease, children [IV.2], [IV.3], and [IV.4] each have a 50% chance of being affected (heterozygous), a 25% chance of being unaffected, and a 25% chance of being affected (homozygous), which would almost assuredly have an earlier onset with more severe symptoms than the 'normal' heterozygous.

Records - Organizing Information

An unlined sketchbook works well for keeping notes and is conducive to drawing quick pedigree charts. A sketchbook with acid-free paper will last a long time and make a great heirloom, and they can be found for less than $20. To back up your sketchbook, take pictures. This works very well.

Most of the raw information, however, will be in electronic format, and it is highly recommended to keep local and remote backups of files, including email and message board postings. A paper copy backup of data is recommended, as well. A 500-sheet ream of acid-free computer paper costs less than $5.

Talking to Relatives

When you first make contact, introduce yourself and the reason for the contact. "We're related <how>, and I'm looking for some information on a rare muscle disease that runs in the family" is a good start.

Email and genealogy site messaging are the quickest and most effective means of making first contact, but always give your phone number and ask for theirs. There is no substitute for talking, so try to have a phone conversation as soon as possible. Information flows much more freely, there's a more human connection, questions or thoughts spring to mind more easily, and people will tell you things they'd never write down.

What doesn't work so well: postal mail. Not a single letter sent through mail resulted in any information; it always had to be followed up with a phone call. It's too easy to let a letter sit, because who responds to real letters any more?

The purpose of talking to relatives is to *elicit information*, so do not argue or overpower the conversation.

A lot of MFM patients do not have an accurate diagnosis. They frequently — and *tenaciously!* — cling to diagnoses given to their parents before MFM was even recognized. If a woman's mother was diagnosed with Inclusion Body Myositis in 1989, then that's what the daughter thinks her mother had. If a man's father was diagnosed in 1990 with Limb-Girdle Muscular Dystrophy, and the son has a confirmed genetic diagnosis of MFM, he might still think he has LGMD and will forward you MDA email about promising LGMD treatments. On the other hand, a deceased relative might have been diagnosed with Post-Polio Syndrome, and it's entirely possible that is correct.

In the near future, whole exome sequencing will be standard and attached to medical records, and there will be no doubt about the presence of known-pathogenic mutations, but the best course now is to just collect information, pass along what is known, and don't argue.

Those who suspect they may have inherited the disease may think there is no value in knowing either way, and even some MFM patients with a confirmed genetic diagnosis will not inform their adult children that the disease is heritable.

The first and foremost goal is to gather information. Matching genetic diagnoses is the eventual goal, but a substantial portion of the work is in finding clusters of relatives with matching symptoms.

Objections to DNA testing

Having DNA confirmation, for both heredity and for MFM confirmation, makes tracking the disease much easier. But there are perfectly good reasons people may do neither.

Objections to autosomal DNA testing for genealogy all boil down to privacy. People will get a DNA test or not; it doesn't hurt to ask, and all they can do is say, "No."

Objections to genetic testing for MFM mutations, however, are much more varied.

By far, the biggest hesitation is due to a very valid concern that having a documented pathogenic mutation will affect the person's ability to obtain or keep insurance (life, disability, long-term care, nursing home insurance), which could be detrimental to their finances. If this is the case, it would be vastly more beneficial and result in better long-term healthcare overall to *not* have a conclusive test.

Sadly, another objection is, "There's nothing doctors

can do anyway, so what's the point?" As mentioned in the first paragraphs, there is still plenty that should and should not be done, whether or not there's a wonder-drug cure.

Some symptomatic relatives have a hyperacute sense of "guilt" about potentially passing along a disease to their children and will not entertain the thought of getting a genetic diagnosis, because they don't want their fears confirmed. They may not tell their doctor that the family has a history of an easily-tested genetic mutation and instead get a fall-through diagnosis of a non-DNA-confirmable ailment whose presentation *exactly* matches the known family MFM phenotype, bullet point for bullet point.

Others may object to genetic testing because, "It's God's will, and whatever happens happens," even though 'whatever happens' happened way back at conception; the future has been with us our whole lives – you already have an MFM mutation or you don't.

Closely tied to that, though, for families with a long history of muscle disease, the 'objection' is that DNA confirmation is irrelevant — it's just part of who you and your family are. When you arrive at a family reunion and see Uncle Bob with a cane, and you notice the foot drop when he walks, it's just, "Well, Uncle Bob has it." Myofibrillar myopathy is no fun, and no one wants it, but in long-running MFM families, it's not really a devastating deal, oddly. You half-jokingly point to Uncle Bob's cane and say, "What's up with that?" And he says, "I'm my father's son," and that's that, and you fill up your plates and go sit down and talk politics.

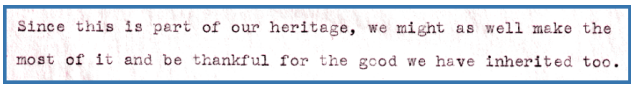

Since this is part of our heritage, we might as well make the most of it and be thankful for the good we have inherited too.

Figure 12 Note from family member with a long history of MFM.

A lesser partial 'objection' to DNA confirmation comes via those who have read "The Immortal Life of Henrietta Lacks"[20] and are concerned about contributing information that may result in no treatment for themselves, but that someone else may profit from. This objection isn't weighty enough to prevail, though it may be mentioned.

The last objection concerns the ever-present shadow of eugenics, and those who think it's their right to state who should or shouldn't exist. The earliest extensive pedigrees of families with Huntington's Disease were explicitly collected for this purpose.

Death Certificates and Medical Records

Death certificates provide good clues about the probability of relatives being affected with MFM and indicate which genetic branches should receive higher priority investigation. Death certificates and related history can also help determine a lower likelihood.

For example, consider a branch that has been traced up to a couple who died over a hundred years ago, and nothing is known except that the man drowned at age 38, and the woman worked a farm by herself until death at age 88. The man may or may not have had a late-onset MFM; he died before he was likely to show any symptoms, and his death can't be definitely tied to any muscle problems. The woman may or may not have had MFM, but it is *incredibly* unlikely; MFM patients have a hard enough time just walking up a driveway, much less running a farm. In this case, it would be more fruitful to prioritize spending time researching the man's siblings and parents, and not the woman's.

Myofibrillar Myopathy is a relatively new disease classification, and any death certificates before the year 2000 wouldn't mention MFM at all; they could list only the most likely diagnoses known at the time. Some neuromuscular diseases mentioned in confirmed MFM cases are:

- "Muscular Dystrophy" (not terribly incorrect, but vague)
- "Limb-girdle muscular dystrophy"
- "Inclusion Body Myositis"
- "Progressive muscular dystrophy, adult onset"
- "Charcot-Marie-Tooth"
- "Rod Myopathy" / "Nemaline Myopathy"
- "Familial Myotonia"
- "Progressive Muscular Atrophy (Duchenne-Aran)"

Online genealogy sites are the simplest for bulk analysis, followed up by requesting any death certificates or other information from relatives. Requesting and paying for government-issued copies is most likely not beneficial or cost-effective.

Online genealogy services routinely add new data sources, including death certificate databases, so it's worthwhile to review occasionally for new additions.

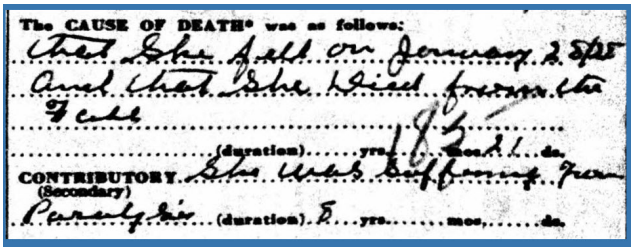

The CAUSE OF DEATH* was as follows:
that She fell on January 2 1915
And that She died from the
Fall
(duration) yrs. 1 mos. 2 da.
CONTRIBUTORY (Secondary) She was Suffering from
Paralysis (duration) 8 yrs. mos. da.

Figure 13 Death certificate sample with a possible – but not conclusive – clue. "The cause of death was as follows: that she fell ... and that she died from the fall. Contributory: She was suffering from Paralysis [8 years]."

ICD Codes

International Classification of Disease ("ICD") codes are standardized numerical index for a large number of com-

mon diseases and afflictions, now primarily used for medical billing. They may be written on death certificates, but are redundant, as the cause of death is spelled out anyway. Where ICD codes are particularly useful in genealogy research is with "death indexes" that are just compendiums of deaths, listing ICD codes, but not actual death certificates.

Search the Internet for tutorials on "'ICD codes' and 'genealogy.'"

http://www.wolfbane.com/icd/index.html

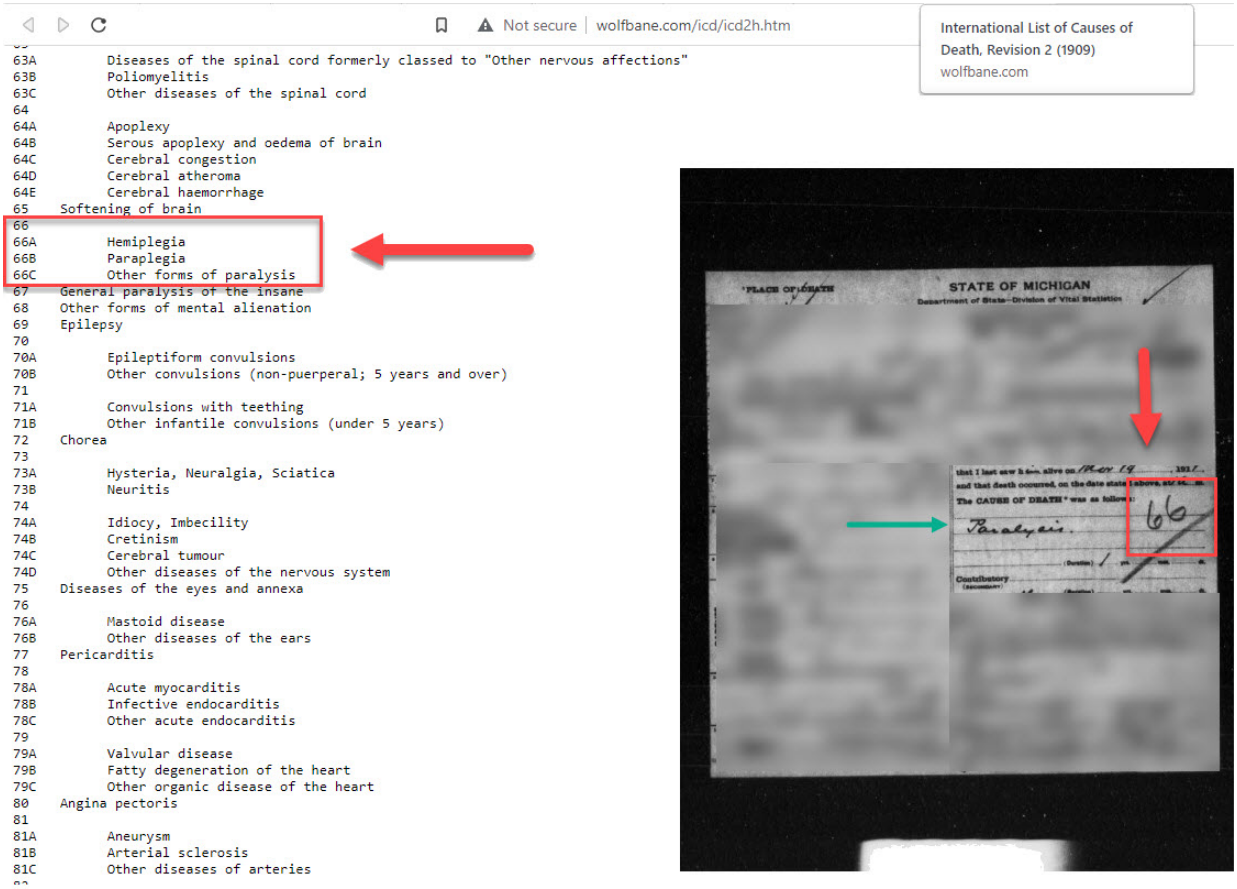


Figure 14 1910 death certificate, where the '66' ICD code matches listed cause of death as 'Paralysis.' ICD2 (effective in 1909) marks '66' as ('Hemiplegia, Paraplegia, and Other forms of paralysis').

If you're on good terms, people will sometimes send you medical records.

Obituaries

Obituaries are often a wealth of information; always search for them. Even if cause of death or medical problems aren't noted, obituaries almost always include the "survived by" relatives, to expand your contact list.

An especially interesting trend was among obituaries in the last half-century where the family suggests donations to the Muscular Dystrophy Association. After listing the descendants of a suspected MFM relative, Internet searches for obituaries can yield quick results for a small amount of effort.

Example Google search: (intext:"John Smith" May 1955 intext:"obituary" intext:"Muscular Dystrophy")

It's rare that anything more explicit is said, but there are exceptions ("He was diagnosed with Muscular Dystrophy and was confined to a wheelchair.").

A large fraction of obituaries don't mention medical problems, but it's worth investigating for the ones that do.

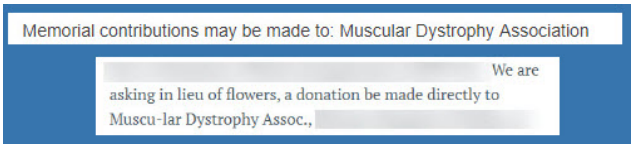


Figure 15 Adjust Internet searches for obituaries where "Muscular Dystrophy" is mentioned.

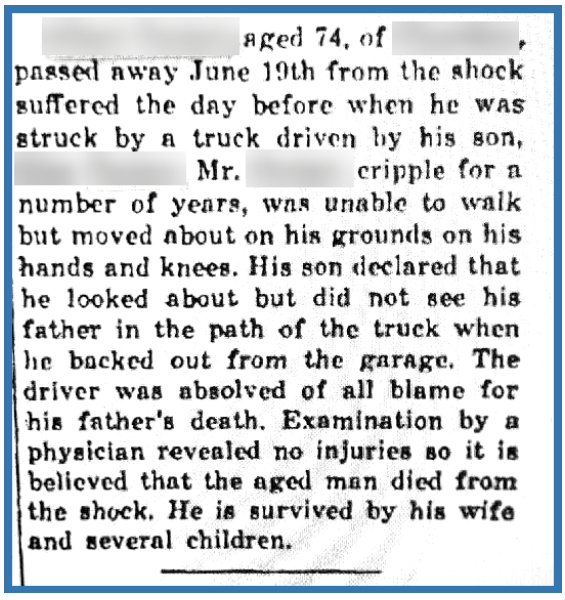

aged 74, of ,
passed away June 19th from the shock suffered the day before when he was struck by a truck driven by his son, Mr. cripple for a number of years, was unable to walk but moved about on his grounds on his hands and knees. His son declared that he looked about but did not see his father in the path of the truck when he backed out from the garage. The driver was absolved of all blame for his father's death. Examination by a physician revealed no injuries so it is believed that the aged man died from the shock. He is survived by his wife and several children.

Figure 16 Newspaper record of MFM death.

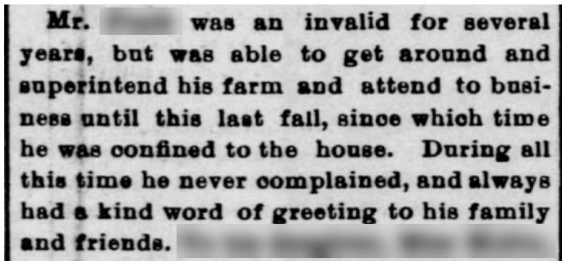

Mr. was an invalid for several years, but was able to get around and superintend his farm and attend to business until this last fall, since which time he was confined to the house. During all this time he never complained, and always had a kind word of greeting to his family and friends.

Figure 17 Newspaper record of MFM death.

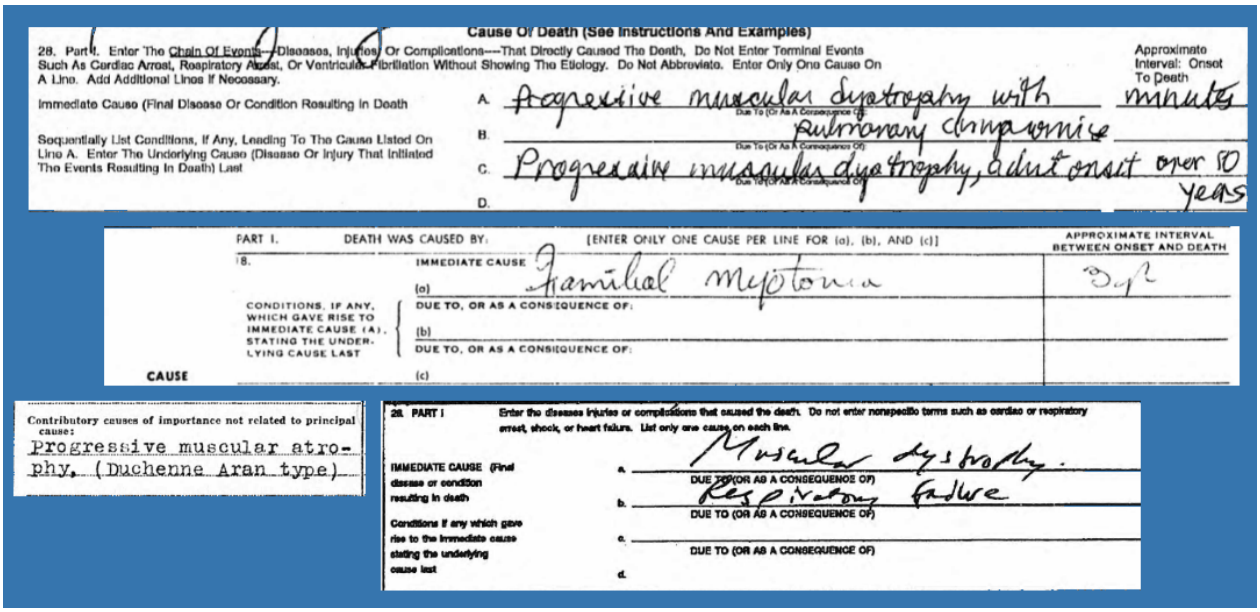


Figure 18 Death certificates samples of known MFM.

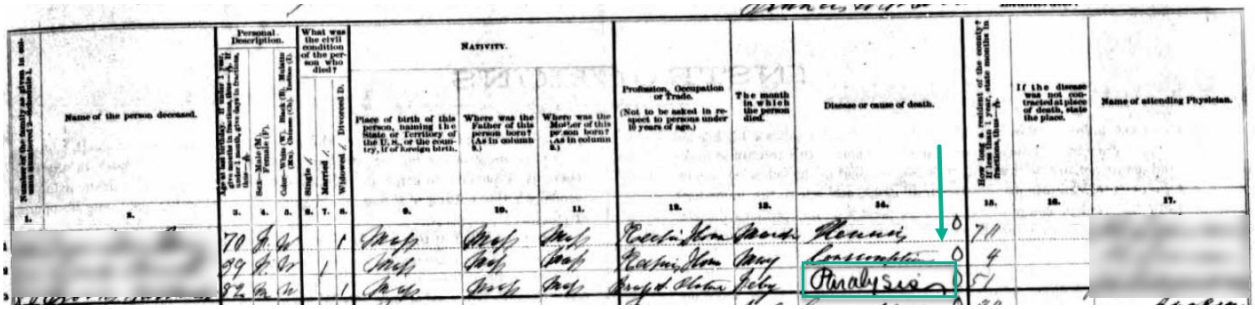


Figure 19 "Death record" index showing "Disease or cause of death" as 'Paralysis.'

Finding others with a specific mutation

If the MFM mutation is known, you'll want to find others with the same mutation, whether they're identifiably related or not. Finding someone else with the same mutation might show you're related (might not) and help find even more affected relatives.

Reminder: do *not* approach family members by mentioning a specific mutation. Only mention this in places where others already know which MFM mutation they have.

Summary Review

MFM is incredibly rare; 99% of doctors have never seen it and don't have the first idea about treatment. You are going to have to be your own advocate, doing what you can with the resources you have. At the very least, this includes documenting your disease progression and attempting to locate relatives who share the same disease. Doctors will not do this; they have no motivation to work on your genealogy.

The checklist here is the quickest way to find results, if any are to be found.

Please provide any feedback to: genealogy@mfm4.org

Appendix: Searching US Census Records

US federal census records have provided a few hints, especially when searchable, as via Ancestry.com. There are free-form entries made by census takers (e.g., 'disabled'), while a couple censuses (1880 and 1940) have specific fields for 'disabled' or 'unable to work.' There are plenty of reasons people may have been disabled or bedridden (e.g., stroke, or farming accident, or numerous maladies), but they give possible indications.

Keywords to search for: "invalid," "disabled," "paralysis," "paralyzed," "crippled," "cripple," "crippel [sic]," "lame," "bedridden," "dystrophy," "atrophy," "myopathy [will also get hits for 'cardio myopathy']," "myotonia," "myositis," "muscle disease," "progressive muscle," etc.

The census records are finite, so a meta-analysis is possible.

Census year highlights:

- **1880** - Checkbox for ("Maimed, Crippled, Bedridden, or otherwise disabled" / "Disabled")
- **1890** - "Over 99% of the 1890 U.S. census was burned in a Commerce Department fire in 1921; of the 62,979,766 people enumerated in the census, the records of only 6,160 survived the fire." [https://support.ancestry.com/s/article/The-1890-U-S-Federal-Census]
- **1940** - "Code E": "U" = "Unable to work")
- All years may include free-form notes under 'Occupation' or other

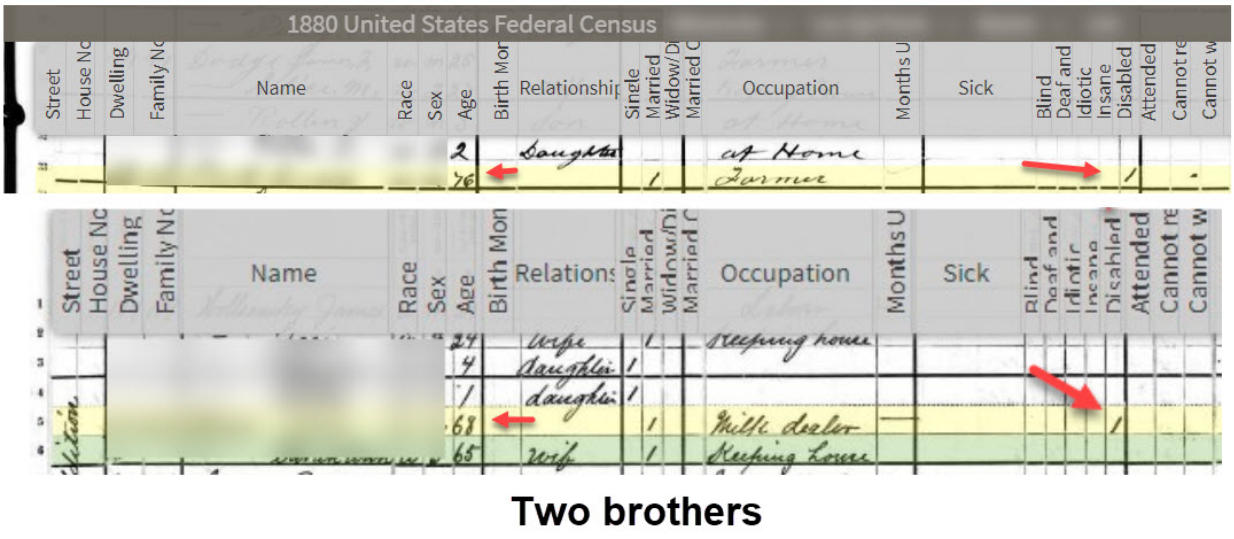


Figure 20 1880 US federal census for two brothers in a known-MFM family.

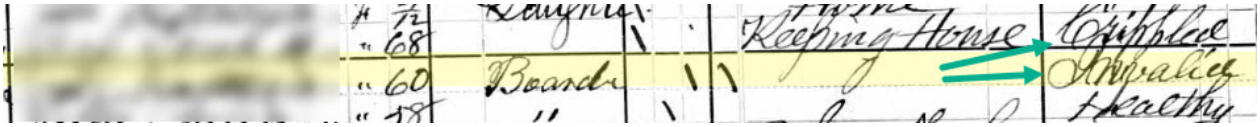


Figure 21 Census record of two people noted as being "Crippled" and an "Invalid."

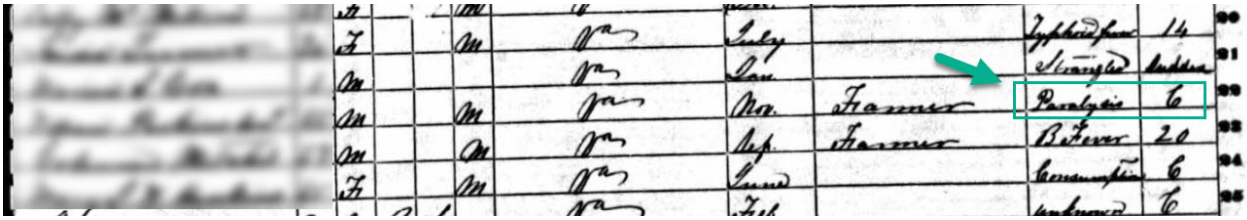


Figure 22 Census annotation of a farmer suffering paralysis.

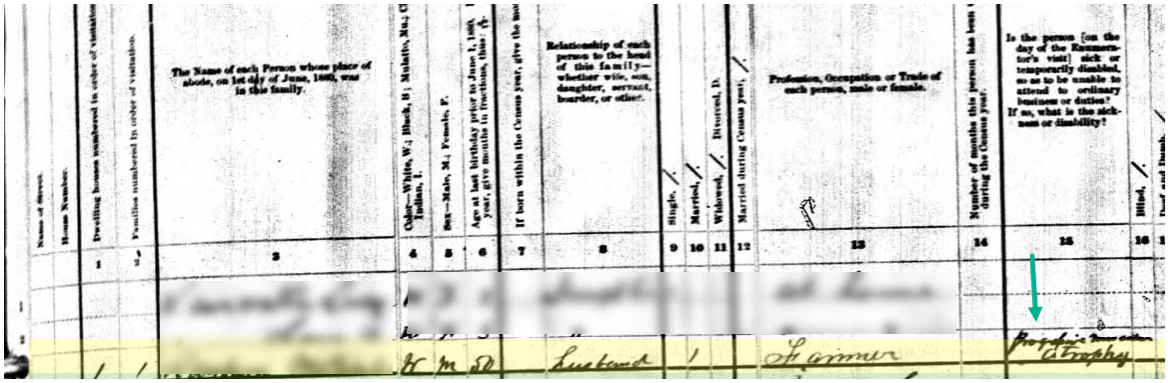


Figure 23 Census record of someone with 'Progressive Atrophy'

Appendix: Historical Examples

Several historical examples of rare disease pedigrees provide some guidance and inspiration.

The "Royal Disease" (Hemophilia B)

Hemophilia B is known as the "Royal Disease," due to its prominent historical impact amongst Queen Victoria's descendants in British, Spanish, German, and Russian royalty.[8] Queen Victoria's "Royal Disease" included only four affected generations and in 2009 was identified as Hemophilia B see[15] Figure S1.

Newer Hemophilia B research[9] shows that ~51% of cases are *de novo*, with "[m]utation ages ... estimated at 2–23 generations."

"Of the 45 haemophilia-B patients registered at the haemophilia centre in Malmo, Sweden, 24 are the sole members of their families to be affected, and in 13 of these 24 cases, ascendant relatives are available for study. Detection of the gene defect showed the mutation to be *de novo* in the proband in 3 of these 13 cases, and inherited from a carrier mother in the remaining 10 cases."[10]

Myotonia congenita

"Twelve patients belonged to a large family (A), which could be traced back to the late 18th century, originating from western Lapland."[3] A larger 14-generation pedigree is referenced in "Myotonia congenita and syndromes associated with myotonia. Clinical genetic studies of the nondystrophic myotonias."[13]

Huntington's Disease

George Huntington "On Chorea" - http://www.kumc.edu/Documents/neurology/Huntington,%20George2.pdf

"The *hereditary* chorea, as I shall call it, is confined to certain and fortunately a *few* families, and has been transmitted to them, an heirloom from generations away back in the dim past."

Nancy Wexler, in an advocacy paper well worth reading: "The Venezuelan HD kindreds encompass 18,149 individuals spanning 10 generations, of whom 15,409 are living and 78% are younger than age 40. There are 9,162 males, 8,256 females, and 731 individuals for whom we do not have gender information. There are 83 unique kindreds. The majority of individuals, 14,761, belong to the main kindred, tracing their origin to a single founder, appropriately named Maria Concepcion, who lived in a stilt village in the early 1800s. The remaining 3,388 form 82 separate kindreds."[22]

See also Alice Wexler's book "The woman who walked into the sea : Huntington's and the making of a genetic disease"[21]

Myotonic dystrophy type 2

"On the basis of the highly statistically significant LD [linkage disequilibrium] and the extent of LD observed, we estimated the age of the DM2 mutation at ~4,000–11,000 years. These data, taken together with the lack of reports for DM2 in non-European populations, suggest a single (or a few) founding mutation(s) for the DM2 expansion in patients of European descent after the migration out of Africa."[2]

"Taken together, these data suggest a single founding mutation in DM2 patients of European origin. We estimate the age of the founding haplotype and of the DM2 (CCTG) expansion mutation to be ~200–540 generations."[2]

Alzheimer's and Parkinson's

"Hence, founder effects can be identified, and, eventually, it may be possible to date the original (*de novo*) mutation. A few of the recurrent mutations causing autosomal-dominant Alzheimer's disease (AD) have been subjected to the study of a putative founder effect. The most famous one is certainly the Colombian PSEN1 p.E280A mutation. Identity-by-descent analysis of the genomic sequence of 102 individuals originating from Antioquia provided the estimation of the DNM occurrence to 15 generations ago, back in the early 16th century. Another well-known example is the Parkinson's disease-associated p.G2019S LRRK2 mutation, which is known to be present on different haplotypes suggesting different founders. One of them was estimated to have occurred 159 generations ago in a Berber founder."[14]

Oculopharyngeal Dystrophy

"Oculopharyngeal muscular dystrophy. A census of French families and genealogic study [abstract]: The first results of a collaborative study aimed at collecting all French families affected by oculopharyngeal muscular dystrophy (OPMD) and their genealogy are presented. ... The disease has been observed in many countries but to our knowledge no epidemiological studies have been reported so far. However, it is known to be particularly frequent in the French-Canadian community living in Canada and USA. In the present study genealogical researches were carried out in 18 families. Three families were of Italian and two of Armenian origin. Amongst the 13 families of French ascent, 3 familial relationships were found: one from a couple married in 1783. ... Further studies are needed to find out whether there was only one mutation responsible for all French cases or whether several mutations occurred in France, as suggested by the present study. It would be also interesting to ascertain whether there is a parental link between the French and the French-Canadian OPMD patients, the latter considered to be descendants of a couple who emigrated to Quebec in 1634."[7]

Revision History

- 2020 - Initial
- 7/14/2021 - added Appendix on census, added Oculopharyngeal Dystrophy in Historical Examples

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