Silva Ataxia Foundation

A Hopeful Heart

Newsletter

Dear supporters,

We can't thank you enough for joining us on this incredible journey to finding a cure for SpinoCerebella Ataxia 3 (SCA-3), also known as Machado-Josephs disease. Like any journey worth taking, we're sure this one will be filled with many ups and downs. However, with much encouragement from our doctor, Dr. Vikram Khurana, MD, PhD (khuranalab.bwh.harvard.edu) at Brigham and Women's Hospital, we are certain that now is the time to seize the moment and have those ups, make the downs a thing of the past.

It's not only about finding "the" cure, though that is definitely the end goal, but also understanding the disease and making advancements in treatments. These advancements will help improve the quality of life for the thousands of people afflicted with ataxia around the world.

So why has our family decided that "Enough is Enough"? Just a glance at our family tree will be all that's needed to answer that question. (See page 4)

As you can see just in Mom's family tree, SpinoCerebellar Ataxia 3 can be traced back to her Great-Grandmother, Grandmother, Mother and Father, as well as her brother, half-brother, half-sister, and three of her children. In addition to Mom's immediate family, there are/were many aunts, uncles, cousins, nieces and nephews who have also fought this brave and courageous battle against SCA-3.

So now you know why we've decided, "Enough is Enough."

After testing in November 2013, I was officially diagnosed with SCA-3 in January 2014. Through my doctors at Massachusetts General Hospital, I was put in contact with Dr. Vik. Shortly thereafter, with the help of our cousin Susan Leonard, I began working on the family tree, realizing that it would be key in Dr. Vik's understanding of how this disease has plagued our family for generations.

In 2014, Mom's condition had progressed too far along to make it possible for her to travel to Boston resulting in Dr. Vik making arrangements to come to Provincetown. The purpose of this trip was for Dr. Vik to take skin cell samples from not only Mom but also other family members both afflicted and not afflicted with SCA-3. Dr. Vik said at the time it was the largest single-family collection of material he had ever received. After Dr. Vik's visit, Mom made the courageous decision to donate her brain, spinal column and any other necessary organs to further his research after her passing.

A mere three years and three months later on October 30th 2017 our brother Mark passed away after fighting a long battle against SCA-3. He had also made the courageous decision to donate his organs to Dr. Vik's research.

When combined with the advancements in stem cell research and gene-therapy, the donations from Mom and Mark have provided invaluable information for furthering the research of ataxia. This gives us a hopeful outlook for the future for the thousands of people afflicted with ataxia.

Dr. Vik believes that with the advances in stem cell research and gene-therapy, in the fields of all SpinoCerebellar Ataxias, they are closer than ever to solving the long-time mysteries of ataxia. With his encouragement our family has established the Silva Ataxia Foundation in partnership with Brigham and Women's hospital with the hope to find a cure for this disease that has plagued our family for generations.

It is on behalf of all of our relatives and your friends and family members, who may also be fighting this fight against ataxia, that we ask you to join us in finding "the" cure.

"Enough is Enough" - truly.

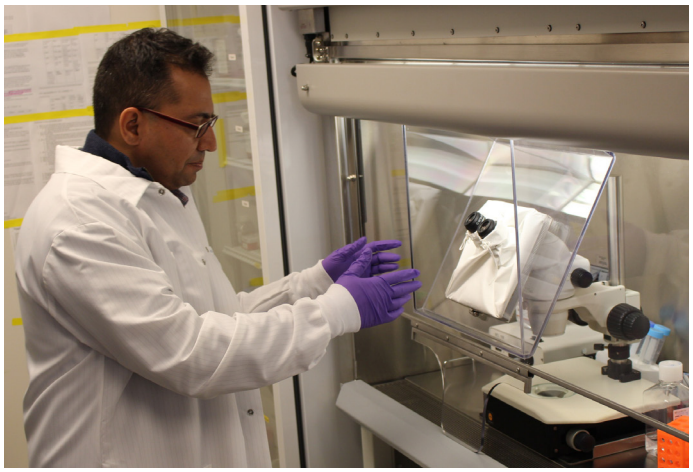
Thank you and God Bless:

David Silva
The Silva Ataxia Foundation

JUNE 2018

What is Ataxia

According to the National Ataxia Foundation, ataxia is a rare neurological disease. It is a progressive, degenerative disease of the nervous system, ultimately affecting a person's ability to walk, talk, and use fine motor skills. Many symptoms of Ataxia can mimic those of being drunk – slurred speech, stumbling, falling, and incoordination. All are related to degeneration of the part of the brain, called the cerebellum that is responsible for coordinating movement. Ataxia is a disease that affects people of all ages. Age of symptom-onset can vary widely, from childhood to late-adulthood. Complications from the disease are serious, oftentimes debilitating, and can be life-shortening. Ataxia is an umbrella term used to classify a group of diseases that include: Ataxia Telangiectasia, Episodic Ataxia, Friedreich's Ataxia, Multiple System Atrophy, Spinocerebellar Ataxia, and Sporadic Ataxia.



Dr. Vikram Khurana MD,PHD- in the Khurana Lab

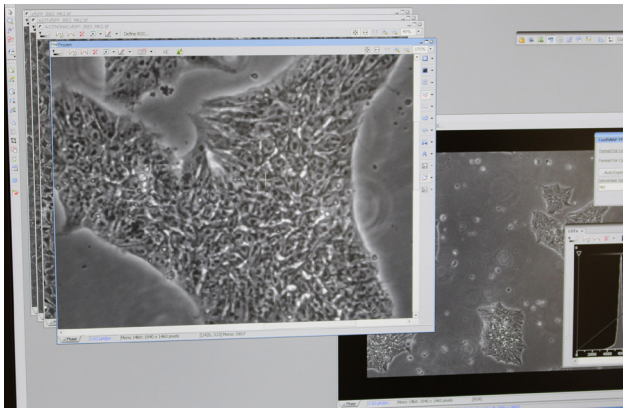
Our Lab Visit

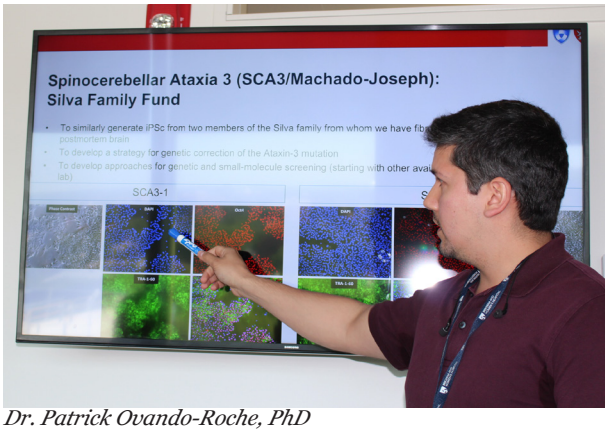
On a beautiful day in May, 2018 we took the ferry to Boston to visit with Dr. Vikram Khurana, MD, PhD, and to see the Khurana lab human stem-cell facility at the Ann Romney Center for Neurological Diseases at Brigham and Women's Hospital. Upon arrival we were greeted by Catherine Young, Director of Development, and after a quick cup of coffee we were taken to the Khurana lab on the 10th floor. There, we were met by Dr Vik and Dr. Patrick Ovando-Roche, PhD. After a brief introduction, we gave Dr. Patrick the history of our families struggle with Machado-Joseph disease.

Dr. Pat then gave us a very passionate and informative talk about his SCA research, what he has accomplished to date, and where he hopes to lead the research.

Our Mom always had hope. Hope that someday all the blood she donated throughout the years would help find a cure. Just months before her death she donated a skin plug to further Dr. Vik's research. Before her death she even agreed to donate her brain to further the research efforts. She always had a hopeful heart.

This one courageous gift has given us much hope that a cure can finally be developed. We find it touching and comforting that our mom continues to spread her hope and love, now living in a small researchers Petri dish.





Dr. Patrick Ovando-Roche, PhD

Dr. Vikram Khurana MD,PHD

The Khurana Lab, based in the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital, uses cutting-edge stem cell, genome-editing and in situ proteomic techniques to study how these hallmark protein-misfolding pathologies are related to genetic factors that predispose to these diseases, and how they may be reversed.

Q&A with Dr. Vik

The following questions, prepared by David Silva, were asked of Dr. Vikram Khurana via email for the purpose of this newsletter and have been edited for clarity and brevity.

Q: How did you initially get involved in neurological research?
VK: I grew up in a household with neurologic disease - for example, one of my aunts with Lou Gehrig's disease, a cousin with multiple sclerosis and multiple family members who died with ruptured brain aneurysms. I also grew up in a family of physicians. When I was an intern in Australia, I began to manage patients with neurodegenerative diseases and felt more should be done. I then took a break from clinical medicine and came in 2001 to Harvard as a Fulbright Scholar to undertake a PhD in neurodegenerative disease research. My focus has remained unchanged since then.

Q: How did you then decide to specialize in Spinocerebellar Ataxia Type 3 (SCA-3)?
VK: As a neurology resident, I became interested in Movement Disorders. I also became interested in using stem-cell technologies to understand and treat neurologic diseases. Our highest chances of success with this new technology were with familial degenerative brain diseases, and within movement disorders, spinocerebellar ataxias represent a very prominent group of diseases. Fortunately, I was a Fellow at Massachusetts General Hospital where Jeremy Schmahmann followed a large number of patients with SCAs. Among these, in New England, SCA-3 is the most common. And, of course, when I met the Silva family I was very moved and inspired even further to make a difference to patients with this disease.

Q: Can you summarize what you have been able to accomplish with both Mom and Mark's donations of their brain, spinal column and organs?
VK: We have so far generated induced pluripotent stem cells (iPSC) from their skin cells. These cells are like embryonic stem cells and can be used to generate brain cells "in the dish". When we find defects in these cells, we need to validate our findings in brain and spinal cord tissue from patients. That is why their donation of these organs is so valuable.

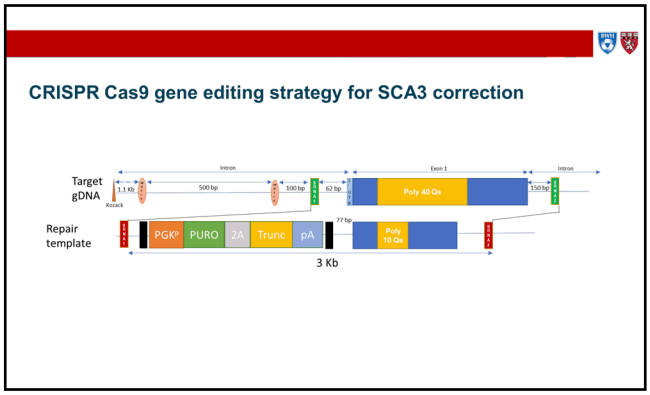
Q: When I saw you in April of 2018, I had asked you about CRISPR*. It's super exciting, can you discuss your intentions on getting to that point with CRISPR and the challenges you're facing writing the replacement strand for CRISPR?
VK: We are developing strategies now to "edit" the genomes (with "CRISPR") of these cells to correct the SCA-3 mutations. In that way, we will have the patient cells compared to the exact same cells with the mutation corrected - we can thus be sure that any defects we note in these cells (that we would like to reverse with gene or drug therapies) is specifically attributable to the actual SCA-3 mutations. CRISPR is particularly difficult for long repeats of DNA like you see in SCA-3 that is caused by multiple repeats of three-letter sequences of DNA (CAGCAGCAG...) so we need to confirm a strategy that works.

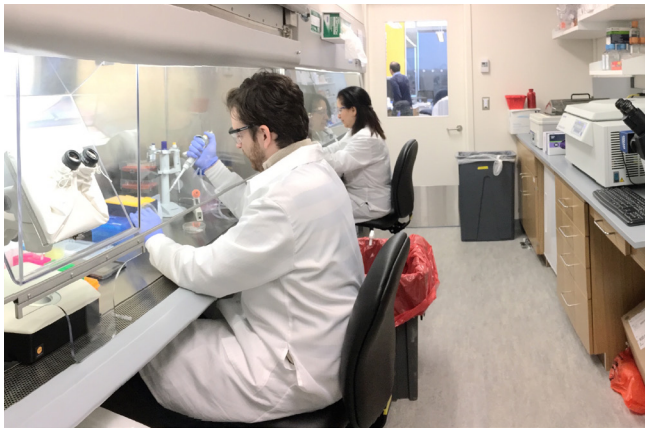
Q: I've noticed from our family's history there are different ages when symptoms of SCA-3 first appear. Is it unusual for this to vary in one family? I've also noticed it plays no favorites as far as effecting men or women, is that true?
VK: There are no hard and fast rules here, but there are differences as you note related somewhat, though not completely, to length of repeats. Generally, the longer the repeat length of the gene is, the earlier the age of onset will be.

Q: What are the best things afflicted individuals can do to help keep themselves strong as the disease progresses?
VK: I think it's very reasonable to employ certain types of exercise - balance and aerobic. There is abundant data in humans and animal models that these exercises make a significant difference in slowing down the progression of SCAs and other neurodegenerative diseases.

Q: Why should people with SCA-3 be encouraged by today's research?
VK: I think stem-cell technologies and genome-editing offer a truly unprecedented opportunity to both examine the disease as it develops (instead of post-mortem, after a patient has passed away) and to intervene. This is the era when genome-editing will meet neuroscience, and diseases like SCA-3 in which the gene is identified stand the best chance of benefiting.

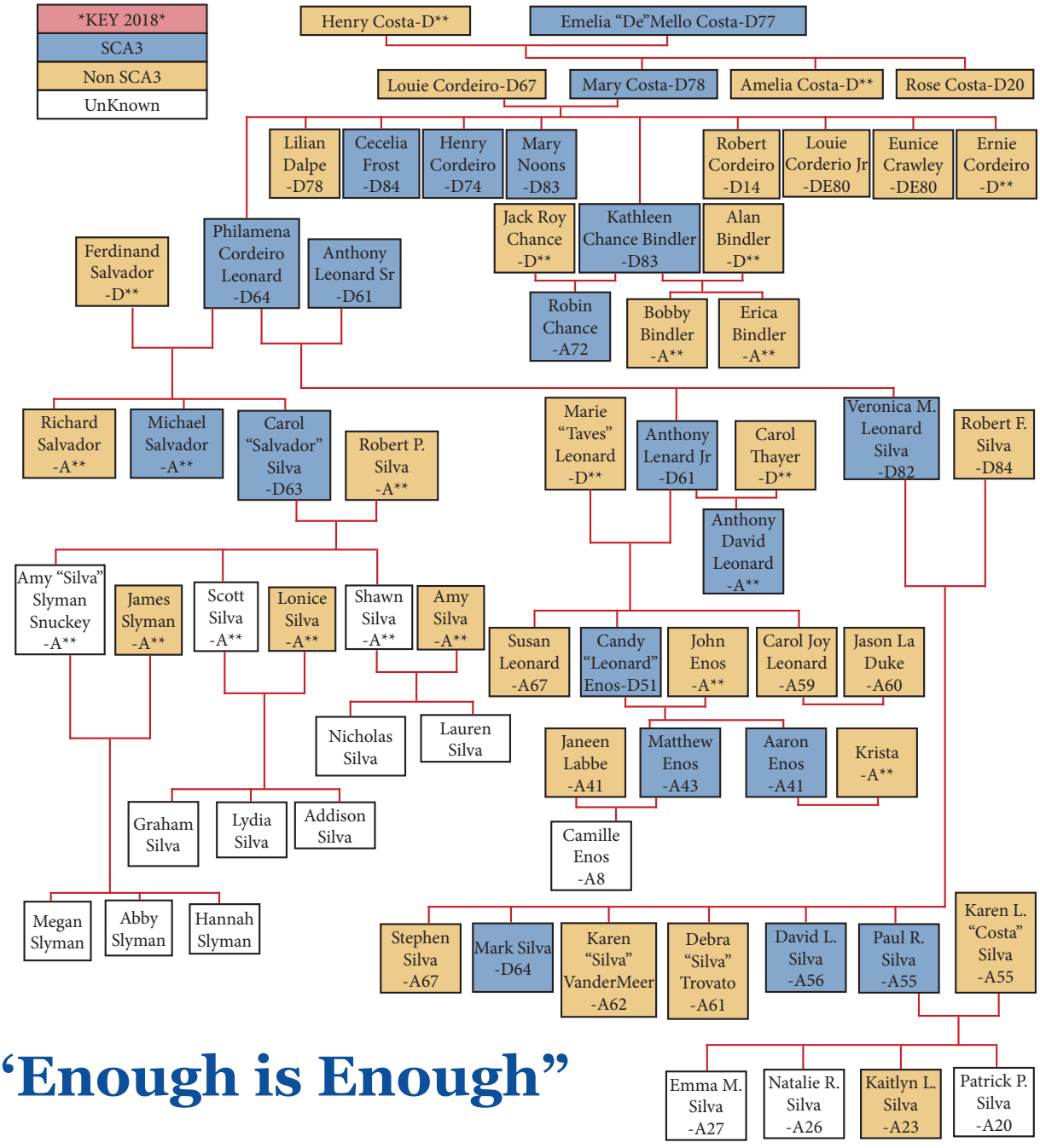
**CRISPR (Clustered Regularly Interspaced Short Palandromic Repeats) technology was adapted from the naturally occurring genome editing system in bacteria and is a simple, yet powerful tool used for editing genomes.*





Investigators at the Ann Romney Center for Neurologic Diseases, working within the Khurana lab human stem-cell facility.

Our Family Tree



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