A Mother’s Story: Fighting Rett Syndrome Head On

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JUST PAST 10 PM on October 10, 1996, I held in my arms the most delicate and beautiful baby girl I had ever seen, my precious daughter. My husband and I had been married almost 10 years but because of my taxing restaurant business and his graduate school commitments we opted to postpone having children. With school done and the restaurant sold we welcomed Chelsea, our first child, and the first grandchild on both sides of the family. Needless to say she was eagerly awaited and bestowed with boundless love and attention.

She arrived three weeks early with perfect Apgar scores and an insatiable appetite. We went home on schedule two days after her arrival. Joy-filled days turned into weeks and then months. We were thankfully, blissfully naive of what was to come.

SOMETHING IS AMISS
The first subtle hints that all were not right surfaced around 6 months. I wrote the following in a journal I was keeping:

April 19, 1997
…I have noticed that you never cry when you accidentally bump your head or I accidentally scratch you during a diaper change. I think you might have a high pain threshold.

A month later there were more unusual signs.

May 19, 1997
…When you are a bit tense you pull your arms in and do a funny thing with your hands …you make a fist and rotate your hands at the wrist …. You have always startled easily. When something or someone gets too close for your comfort you close your eyes. Lately the garage door startles you. Whenever you hear it you tense up and flail your arms and legs ….

By the time Chelsea was almost a year old the nervous knot in my stomach was becoming harder to ignore.

September 22, 1997
Sometimes you bite people when you are frustrated. But yesterday you bit yourself. You left four bite marks on your forearm. You didn’t react at all. No crying, no yelp … nothing.

October 2, 1997
Grandma recently pointed out that you don’t do any typical baby things: you don’t take a bottle or a pacifier, you don’t have a favorite stuffed animal or blanket, you don’t take naps, you don’t crawl. I have also been pondering your personality. I find it strange that you are content to sit (and not crawl). You are a very curious and observant baby and yet you don’t explore the things that are just out of your reach …. You have been very cranky lately. I don’t know what is wrong. You cry often, you are very clingy, you want to nurse all day.

When Chelsea was 14 months old I wrote in the journal:

It is now quite clear that you are not doing some things that are typical for your age: you don’t point with your finger, no self-feeding, won’t drop objects in containers, won’t pull to standing. We have an appointment with a neurologist soon to rule out any serious reasons for your developmental delays.

This was to be one of the last entries as I could no longer bear to write sad words in a journal that was to chronicle milestones and achievements.

Chelsea was clinically diagnosed with Rett syndrome 10 months later, just a few days after her 2nd birthday. A year later, when Dr. Huda Zoghbi at Baylor College of Medicine identified the “Rett gene,” MECP2, Chelsea was among the first to

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have the diagnosis confirmed genetically. She has the most common mutation, T158M, which accounts for about 10 percent of all cases.\textsuperscript{1}

Receiving Chelsea’s genetic confirmation came as a relief. By that point I was fully invested in Chelsea’s Rett diagnosis. Had the lab results come back negative we would have been back in “limbo land.”

I had spent the interim year between the clinical and genetic diagnosis on the phone. I spoke to academic and industry scientists, NIH staff, clinicians, and parents who had started research foundations. Every person I spoke to recommended two or three other people to connect with and via this ripple effect my network quickly grew.

I sometimes think back to those calls, which now generate a rather queasy feeling in my stomach. I was speaking to scientists and industry leaders who were tops in their respective fields. I had only AP biology and chemistry and a few college science classes to fall back on. At the time I was too desperate to be nervous. Remarkably, every single person I spoke to or met with was compassionate, respectful, and, most importantly, helpful.

THE LAUNCH OF RETT SYNDROME RESEARCH FOUNDATION AND RETT SYNDROME RESEARCH TRUST

By the time Dr. Zoghbi announced in 1999 that the genetic cause of Rett syndrome had been discovered, I was on the verge of launching a research organization, the Rett Syndrome Research Foundation (RSRF), with a handful of like-minded parents. The timing could not have been more fortuitous. The MECP2 discovery blew the Rett syndrome field wide open, and esteemed scientists such as Adrian Bird and Rudolf Jaenisch were becoming involved.

In 2001 the first mouse models were published and quickly became available to the scientific community.\textsuperscript{2,3} For a number of years, RSRF began funding numerous $100,000 grants. At first the focus was genetics, understanding genotype–phenotype correlations. In time the attention shifted to include biochemistry and then neurobiology. By the mid-2000s we were receiving over 100 applications for every request for proposal and funding about $2 million a year in research.

The next breakthrough happened in 2007 when Adrian Bird, who had cloned MeCP2 in 1992, published in \textit{Science} that the symptoms of Rett in mouse models were dramatically (and unexpectedly) reversible even in late stages of the disease.\textsuperscript{4} It was truly surprising that a disorder thought to be developmental could be tractable. The news sent shockwaves through the scientific and family community alike. It reinvigorated the search for potential treatments and infused the community, both researchers and families alike, with a renewed sense of urgency.

That same year the RSRF merged with an older family support organization, the International Rett Syndrome Association, and became the International Rett Syndrome Foundation. Yearning for the freedom to focus exclusively on research and to pursue scientific directions I felt were critical, I left and founded the Rett Syndrome Research Trust (RSRT).

THERAPEUTIC STRATEGIES

At the end of the first scientific workshop that RSRT hosted in 2008, I scribbled on a whiteboard all the various strategic therapeutic approaches that were either being pursued or that could be pursued. I think it was the first time that I and the scientists and clinicians in the room had visualized all these options together.

The initial stick figure graphic was quite simplistic; Fig. 1 shows the state of therapeutic approaches being tried in animal models today.

Since Rett syndrome is caused by defective \textit{MECP2}, it stands to reason that approaches that attack the root cause, \textit{MECP2} itself, hold the greatest promise of profoundly improving symptoms. Therefore, approaches on the left side of the graphic can be classified as potentially curative. On the other hand, therapeutic interventions that are downstream of \textit{MECP2} will likely improve a symptom or subset of symptoms. These approaches are treatments rather than cures.

This commentary will focus on gene therapy approaches for Rett. But I will briefly just mention the other strategies targeting \textit{MECP2}. Since \textit{MECP2} is on the X chromosome and all females have two X’s, beside each active mutated gene rests a healthy but silenced backup gene. If we could reactivate \textit{MECP2} in enough cells, we could conceivably reverse Rett symptoms.

About a third of all mutations are nonsense mutations that are amenable to compounds that can read through the premature stop codon. Although this is an area that RSRT is keeping a close eye on, I, unfortunately, don’t see dramatic progress taking place.

Protein replacement is a strategy that few to date have embraced for Rett. However, with an increasing number of platforms to get proteins into the brain, this is an area begging to be explored. We know from animal studies and from the human \textit{MECP2} duplication syndrome that too much MeCP2
protein is detrimental. Dosage may therefore be more easily titratable using protein replacement than gene therapy. Since MeCP2 has a nuclear localization signal, it should be able to enter the nucleus, assuming that we can deliver the protein into brain cells.

GENE THERAPY FOR RETT

Ever since the MECP2 gene was identified as the leading cause of the disorder, the possibility of addressing the symptoms with gene therapy has been a tantalizing option: We know our gene, we know that Rett syndrome is not neurodegenerative, and we have the prospect of reversibility.

However, Rett also offers some unique challenges beyond the issue of delivering the payload to the brain. As I’ve already mentioned above, the dosage of MeCP2 must be tightly controlled. Too little leads to Rett syndrome; too much leads to MECP2 duplication syndrome. Hypomorphic mouse models suggest that one might expect to find a continuum of neurological symptoms in between the book ends of Rett and duplication syndrome.

Furthermore, females with Rett are mosaic for the disorder because of X chromosome inactivation. One cell may have the wild-type gene active, whereas the neighboring may have the mutated one active. In the ideal situation, vectors would differentiate between wild type and mutant and only transfect the mutant cells. The final challenge is that we have to distribute MeCP2 broadly throughout the whole brain.

Fortunately, multiple labs took on this challenge. In 2012 Stuart Cobb at the University of Glasgow and Steven Gray at the University of North Carolina at Chapel Hill showed lifespan and symptom improvement in presymptomatic newborn and juvenile male Mecp2 knockout mice using AAV9 delivery of Mecp2.6

A year later the labs of Gail Mandel, Oregon Health and Sciences University, and Brian Kaspar, Nationwide Children’s Hospital, and Adrian Bird, University of Edinburgh, also used AAV9 and showed lifespan and symptom improvement but this time in symptomatic female mice, which are the models that most closely resemble the human disorder.7

These two articles laid the foundation for a gene therapy program for Rett. I began to think about how we could accelerate the collection of data required to move from concept to clinic.

A few years earlier, in 2011, RSRT had launched the MECP2 Consortium, a dynamic collaboration between three powerhouse labs (Adrian Bird [University of Edinburgh], Michael Greenberg [Harvard
University], Gail Mendel [Oregon Health and Sciences University]) tasked with identifying the function of the MeCP2 protein, which despite an intense effort spanning several decades has remained elusive. RSRT's response to solving this complex problem was to convene thought leaders who possess distinct but synergistic expertise; facilitate the necessary infrastructure to enable regular sharing of information; and provide the necessary financial support to give investigators the freedom to follow their scientific instinct. RSRT organizes in-person meetings twice a year for the investigators and lab members and regularly scheduled conference calls in-between the face-to-face gatherings. Bottom line—scientists who were previously competing are now working together to solve a difficult problem.

With the positive experience of the MECP2 Consortium, I tested the waters to see if the labs engaged in gene therapy would be amenable to a similar approach.

My plan was to bring together labs with deep knowledge of the Rett animal models (Cobb and Mandel labs) together with gene therapy labs (Gray and Kaspar). Together, the labs would have the necessary skillsets to determine whether gene therapy is a viable therapeutic option and if so to execute the required experiments to file an IND. We met in person in late summer of 2013 at a JFK airport hotel and decided to pursue the consortium approach. The consortium is now in its third year and the scientists are working on the following in parallel: vector optimization, how much gene therapy to deliver, and delivery route optimization. Although a lot of work remains, there is preliminary encouraging data that an effective design can be achieved.

This readership will likely know about the two ongoing trials using AAV9: one for spinal muscular atrophy trial and the other for giant axonal neuropathy. These trials represent two important “firsts”: the first time that AAV9 was injected into people and the largest amount of vector ever injected. These trials, as well as the burgeoning industry interest in the gene therapy field, give the Rett community great hope that many more trials and treatments will follow.

Today's Rett research landscape is unrecognizable from when I made the first calls to scientists almost two decades ago. The most dramatic evidence of progress is the interest in Rett from pharmaceutical and biotech companies. I'm fielding calls from industry almost on a daily basis. I'm sometimes tempted to pinch myself to ensure I'm not dreaming.

**LESSONS LEARNED**

With 17 years of disease advocacy under my belt I have learned a few lessons:

- Do not fall in love with the science that you fund. To do that means to lose objectivity.
- Stay nimble—new technologies and data must continually be monitored for and embraced when appropriate.
- Don’t become insulated—RSRT is constantly soliciting feedback on “everything Rett”—every article that comes out and every announcement that is made receives a thorough objective and comprehensive analysis.
- Don't accept dogma without proof—data should drive the decisions.
- Surround yourself with smart and creative people—mediocrity won’t cut it.
- Build it and they will come—whether you are starting a foundation or launching a major project, don’t think too far in advance or you may lose your nerve. One step at a time.

Effective disease nonprofits bring a lot more than just money to the table. They bring laser focus on treatments and cures and an innate sense of urgency. They bring a big-picture perspective. They identify the knowledge gaps and figure out how to fill them. They realize that focusing on clinical research such as natural history studies, outcome measures, and biomarker development is equally important to basic science. They recruit scientists and clinicians into the field and foster collaborations, not by imposing but by nurturing.

Between the two organizations, RSRF and RSRT, and with the enormous support of committed trustees, staff, and affected families, I've helped to raise almost $50 million. I've had the great fortune of benefiting from a vast network of advisors and a handful of sage scientific mentors (you know who you are). With their guidance we've invested over $47 million in research.

Chelsea, aged 19 now, is no better for it. She is in a wheelchair, is unable to speak, has zero use of her hands, suffers from intractable seizures, and is fed through a feeding tube. She is, however, so much more than this laundry list of symptoms. She is the heart and soul of our household. One brilliant smile from Chelsea has the power to chase away stress and sadness. When treatments and a cure come—and I do not use the word “cure” lightly—I fervently hope that she too will reap some benefit.
REFERENCES


