VIEWPOINT

Reaching out to families can inspire new autism research

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In July 2015, more than three dozen researchers gathered in a bland hotel meeting room in Orlando, Florida, for the first day of a science conference on dup15q syndrome.

This condition, which results from a duplication of a portion of chromosome 15, causes **epilepsy**, intellectual disability and autism. Every two years, an advocacy group for people with the syndrome called the **Dup15q Alliance** brings together scientists studying the syndrome to share ideas and discoveries.

As I approached the podium to give my talk, I scanned the audience. Here was a bunch of incredibly smart and eager investigators trying to unravel the mysteries of this syndrome. Some of the researchers study preclinical models of epilepsy, others the molecular effects of having too much **UBE3A** protein, which is encoded in the duplicated region.

I asked the audience if any of them had ever met an individual with dup15q syndrome. Less than half raised a hand.

As it happened, the Dup15q Alliance was sponsoring their family meeting in the same hotel. I had attended this gathering two years earlier, when I had experienced an incredible event known as the ‘family parade.’ I knew that today’s family parade was about to begin.

I decided that my talk, which was supposed to be about **biomarkers** of the condition, would pale in comparison to the family parade. I suggested that we put aside our laptops and take a detour. We walked as a group down the stairs and through the lobby to the main ballroom.

‘Please find a treatment’:

We filed in as people from across the world greeted one another in excited, hushed voices. We stood along a wall, observing as the parade got underway. The first person to traverse the center aisle, surrounded by hundreds of people seated on folding chairs, happened to be someone I had seen in my clinic. As his mother proudly pushed his wheelchair, he smiled and waved, and the crowd cheered. The master of ceremonies announced the young man's name as his photo flashed on a screen at the front of the room.

As the parade continued, the many features of the condition revealed themselves in a way that no case series, cohort study or video presentation could ever capture. We saw school-age children holding their parents’ hands, beaming with joy as they marched unsteadily, the ataxia (poor motor coordination) evident in their gait. Some children needed encouragement from their parents because of their tremendous **anxiety**, another manifestation of the syndrome. There were adults being pushed in wheelchairs who did not have enough head control to gaze at the audience, and newly diagnosed infants being carried by mothers who exuded both gratitude and trepidation about joining this community.

Some of the attendees of the science meeting appeared wonderstruck; others shed tears. When the parade ended, I introduced some young neuroscientists to the families I knew. The families expressed appreciation for the scientists’ efforts and urged them to “please find a treatment.” For

a few moments, we were all one community, gathered for the same goal, albeit with incredibly different backgrounds, experiences and perspectives.

We returned upstairs to resume our conference, and as the day went on, many speakers referred to the events of the morning. They generated new ideas based on observations they had made at the parade. To mention a few: What is the neural basis of the muscle weakness known as hypotonia that afflicts so many people with dup15q? How early in a child's life can this trait be measured? Is it possible to quantify the severity of the motor impairments by using preclinical models such as fruit flies or mice so that we can then test potential treatments?

For me, the remainder of the scientific meeting felt infused with purpose and a sense of reverence for the problems we were trying to solve.

Clinical insights:

Medical research is often thankless. Investigators face constant rejection — from journals, peers and funders. I've seen scientists so discouraged that they leave academia. It is critical to create opportunities for biologists and other basic researchers — particularly students and early-career investigators — to meet and learn from the people they are ultimately trying to help, even if the path from their scientific endeavors to the clinical population seems long. This connection can help underscore why the work matters.

These clinical connections can also inspire new investigations. In fact, contact with families has driven my research agenda throughout my career as a pediatric neurologist.

As a neurology resident at Boston Children's Hospital 10 years ago, I was evaluating children with genetic syndromes, such as tuberous sclerosis complex (TSC), that confer a high risk for autism. The parents, many of them up-to-date on the latest research, were eager to find out whether their babies, who were newly diagnosed with TSC, showed early signs of autism. We had no screening algorithms for these infants, so parents were often told to bide their time. In the cases in which an autism diagnosis later emerged, they understandably felt they had lost months or years when their children could have received interventions.

To address this major gap, my mentor **Charles Nelson** and I designed a study to evaluate the both early behavioral and brain-based markers of autism in infants with TSC. We found that these babies do show signs of autism in the first year of life[1,2,3]. That work helped tremendously with early diagnosis, but it led to the next major gap: early intervention. Parents began to ask us: What should be done once early signs are detected? Based on this question, we designed and began the first randomized **controlled clinical trial** of early behavioral intervention for these infants.

Similar inspirations have emerged in dup15q syndrome. Clinical observations of altered electroencephalographic (EEG) patterns in children with the syndrome led us to quantify a

biological marker of the condition. That biomarker is being considered for use in clinical trials of drug treatments for this condition[4].

Bedside to bench:

How can scientists who don't treat individuals make these connections? At the Care and Research in Neurogenetics (CARING) clinic at the University of California, Los Angeles, we have begun a monthly teaching conference dubbed "Bench to Bedside." This meeting begins with a description of a specific person or group of people seen in the clinic and then proceeds to a research presentation related to that person's condition. The talks attract students and faculty from across neuroscience, neurology and psychology.

We also have a program in which neuroscience graduate students can shadow a person and his or her family as the person goes through an afternoon of assessments at the clinic. (We always ask permission from individuals and their families first.) Sometimes visitors observe through one-way mirrors in an adjoining room so that their observation is less intrusive.

One of my neuroscience graduate students, whose work is focused on EEG biomarkers of dup15q syndrome, had never interacted with one of these families before joining my lab. She had only reviewed EEGs. She began by shadowing people in the clinic and, before long, she was assisting in conducting some of the pre-clinic interviews with families. After hearing from these parents about their children's sleep problems, she became interested in the possibility that their sleep EEG might be unusual. She looked more closely at the sleep-related EEG data, and the early results have been quite exciting. That work has become the centerpiece of her dissertation and may inform treatment targets in trials.

I feel so grateful to be a physician-scientist, as the people I see in our clinic continually motivate my research and compel me to keep persevering, even when the journey feels daunting. No one doubts the benefits to research when scientists meet face to face, but I would argue that there is even more value to the impact of scientists spending time with families. Our goal is by no means to transform neuroscientists into physicians, but rather to enhance their sense of purpose and inspire work that could fundamentally alter the course of these conditions.

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