OPINION, **Q&A**

Questions for Katherine Rauen: Cancer pathway's autism link

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Costello syndrome: Helaina has a rare neurodevelopmental disorder that has been linked to autism.

Cancer and autism have a surprising number of genes in common, including **one key pathway** that helps regulate how cells grow and move. Certain mutations in this pathway, dubbed RAS, make cells grow out of control and are responsible for about one-third of all human cancers.

In the past few years, several studies have discovered that autism risk genes influence the RAS pathway. But well before that, hints of a link between RAS and autism were apparent in the clinic, says **Katherine Rauen**, chief of genomic medicine at the University of California, Davis.

Rauen studies a group of rare developmental disorders **called RASopathies** that stem from a single-gene mutation that boosts the RAS pathway. These disorders — neurofibromatosis type 1 (NF1), Noonan syndrome, Costello syndrome and cardio-facio-cutaneous syndrome (CFC) — are characterized by a wide range of symptoms, from an increased risk of cancer to **repetitive behaviors**.

About 15 years ago, Rauen says she noticed that many children with the disorders also have **symptoms of autism**, such as narrow interests and social deficits. In 2013, she and her colleagues showed that roughly one-quarter of children with RASopathies have autism — a prevalence nearly on par with that of the better-known **fragile X syndrome**.

Rauen presented her latest work on RASopathies at the **2015 Keystone Symposia: Pathways of Neurodevelopmental Disorders meeting** in Tahoe City, California, last month. We caught up with her at the meeting to find out why autism researchers should care about these obscure cancer-linked disorders.

SFARI.org: What makes RASopathies so interesting?

Katherine Rauen: The RAS pathway is a critical signaling pathway that controls the basic functions of a cell. It relays signals from outside the cell and controls whether the cell should divide, differentiate or mature. The pathway has been well studied in the context of cancer. So the idea of having all these developmental syndromes that affect the RAS pathway was honestly astonishing to scientists. No one thought that these types of germline mutations — which activate the pathway in all cells in the body — would be compatible with life. It was a big, big deal.

S: When did you first suspect that autism might be associated with RASopathies?

KR: In the early 2000s, I started a RAS clinic at the University of California, San Francisco (UCSF) — which I have since moved to the University of California, Davis — in order to address syndromes that are caused by dysregulation of the RAS pathway. At that time, I would attend all Costello syndrome, CFC and NF1 family meetings.

What intrigued me was a big controversy over whether NF1 is associated with autism. There were numerous papers published on this controversy in the mid-2000s. Based on my clinical observations, there was no doubt in my mind that NF1 is associated with autism. And because of being so involved with the family groups with Costello syndrome and CFC — and knowing the essential role the RAS pathway plays in development as well as I did — there was no doubt in my mind that these children also had features of autism. But I would have conversations with NF1 experts who would adamantly deny it.

Families ten years ago were so frustrated by the results of neurodevelopmental testing for their children. Some would get diagnoses of autism, whereas others might be told that their children had some features of autism, but that it wasn't autism, even though it looked like autism and had all the hallmarks of autism.

S: How did you prove this link?

KR: It was through a collaboration with **Lauren Weiss**, who is a colleague at UCSF. The first time I met her we were at a faculty recruitment dinner at UCSF and she was talking about her autism work. I was so thrilled to meet her and her work was very intriguing.

I remember telling her that I thought RASopathies are associated with autism, and that it's really controversial with NF1, and no one has even looked at Costello syndrome or CFC syndrome. But I told her anecdotally that several of the patients that I knew with RASopathies have a diagnosis of *bona fide* autism. That dinner was really the spark that launched this project.

Laurie and I started to look systematically at the autism traits in all of the RASopathies. Then in 2010, a paper came out in *Nature* **implicating the RAS pathway** as one of the big nodes in autism. I remember thinking to myself, “Well yeah, of course it is.”

UC Regents Katherine Rauen

S: How can an autism diagnosis help children with RASopathies?

KR: It provides the family with a diagnosis that explains the behavioral issues or stereotypical behaviors that these parents had been trying to tell their doctors about for years. A firm diagnosis stops what we call ‘the diagnostic odyssey’ and instead gives parents something they can act on. Just having a ‘correct diagnosis’ is so important to parents seeking answers and treatments for their child. Even though an individual might have a diagnosis of CFC, there may be autism treatments available that might help with their behavior or focus. It opens up a whole new set of potential resources to them.

S: Were there treatments available for behavior problems in these children before?

KR: No, not at all, and it was very frustrating for these families. For example, children with CFC often have very focused and intense interests, similar to those seen in autism. For example, one child with CFC can look at any SUV on the road and know its name, make and model. Another CFC child knows everything there is to know about tractors. Just having this publication come out saying there are autism traits in these children provides the scientific basis for an autism diagnosis,

which may be treatable on top of the diagnosis of the RASopathy.

S: Are there existing drugs targeting the RAS pathway that might help these children, or even children with autism?

KR: Absolutely. I think one of the reasons that our discovery of the CFC genes had such a large scientific impact was that an entire pathway was implicated in this syndrome. Moreover, there are modulating inhibitors that target the RAS pathway available as cancer treatments that could potentially be used in clinical trials for RASopathies. For example, MEK inhibitors, small-molecule drugs that inhibit members of the RAS pathway, are being considered as treatments for NF1.

S: What can autism researchers learn by studying RASopathies?

KR: We know that autism is caused by many different genetic etiologies. We also know that there's a huge environmental component. The RAS pathway plays an essential role in development, including neural development. To understand its important role in autism, one can start by looking at environmental influences that might modulate the pathway. Remember, the pathway relays environmental signals and cues into the cell and regulates the expression of any number of downstream genes. It’s important to think about how regulation or activation of the RAS pathway could contribute to autism. In addition, there are other important pathways that are downstream from RAS — such as the PI3K pathway, also implicated in cancer — that appear to have a role in autism as well.

S: Your story seems to highlight the power of observation. Would you agree?

KR: That's how a lot of things happen in science; it starts with a clinical observation. For example, now we’re following up understanding the developmental mechanism underlying the reduced amount of skeletal muscle in people with a RASopathy. These individuals look like their skin has been stretched over their bones. Understanding these mechanisms will not only provide insight into normal skeletal muscle growth and development, but can be used as a tool in developing treatments for RASopathies, as well as for muscle-wasting diseases.

As a medical geneticist, you are really on the frontlines interpreting what these genetic lesions mean based on observation. There is no field in medicine that is evolving as quickly as genomic medicine. I have seen individuals who had never received a diagnosis for their signs and symptoms despite coming into the clinic for years and years. Now, a decade later, we can

sequence their genes and provide these individuals with a diagnosis. Having a genetic diagnosis is the first step. Understanding the mechanisms and developing a treatment is the next.

I always tell the families I work with that we might not have a treatment or an answer today, but that doesn't mean there's not going to be one down the road.

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