On the Hunt for Modifiers

Monica Coenraads & Dr. Neul Discuss a Newly Funded Project

MC: Hello everyone. This is Monica Coenraads, skyping in from Connecticut. I am the Executive Director of Rett Syndrome Research Trust and I'm speaking today to Dr. Jeffrey Neul. A lot you will probably already be familiar with Dr. Neul . He is the co-director of the Rett Clinic at Texas Children's Hospital. He's currently running a clinical trial and some of many of you may also know him from the natural history study. Good morning Dr. Neul. Thank you so much for joining us and taking time from your busy schedule.

JN: Good morning and thank you for taking the time to talk with me

MC: So today we're going to be talking to Dr. Neul about a new project that RSRT and Dr. Neul are launching and it has to do with the topic that many of you have heard about already: the search for modifier genes. RSRT has been funding for a number of years a project on in the lab of Dr. Monica Justice who is using mouse models to try to identify mutations in other genes that lessen the severity of having no MECP2 or a mutated MECP2. Because the cost of sequencing and has gotten more manageable (cheaper) and also because the bioinformatics capabilities are much greater, we can now start thinking about home looking for modifier genes in human patients. So this project Dr. Neul will be spearheading is going to sequence the exxome of high-functioning children who have any MECP2 mutations but whom wouldn't naturally be diagnosed with Rett because they don't meet the criteria. In the hopes that we might be able to find secrets in their genome that might help other kids because it would open up potential targets for therapeutics. So the three-year project with a $350,000 budget. Let's jump in, Dr. Neul, I'd like to start us off by asking you if you can just tell us a bit about nuts and bolts of this project.

JN: This project really came about because I had found people in my clinic who are coming to see me who were referred because they had mutations in MECP2, common mutations that cause Rett Syndrome, and these people didn't have Rett Syndrome. It really fascinated me why you could have such variation in the clinical presentation. You could have people who maybe were diagnosed with autism or pervasive developmental disorder yet had that same mutation. There are a lot of potential causes and we ruled out the ones we knew like X-chromosome inactivation in these people. That didn't explain it so there must be something more. So I was interested in trying to figure out how to find genetic modifiers. Here Baylor College of Medicine, I was very familiar and initially started helping Monica Justice with her modifier strain in mice a so obviously that's a great avenue, an idea that there are genetic modifiers in Rett Syndrome that may make the phenotype, the clinical features, less severe. If we can find it in mice, I think that idea would be that maybe we can find in people. As you said, the exact details of the technical aspects in terms of sequencing and bioinformatics has advanced dramatically to make this I'm a realistic idea.

So the nuts and bolts of it is that we are through the natural history study, which has been an ongoing project funded by the NIH and IRSF, we've accumulated a very large amount of clinical data on people with Rett Syndrome and so we looked at that and said we can take people who are clinically very severe or very mild, so they are at the ends of the distribution of severity, and try to use those as the subjects to sequence all the genes in their body. Now the issue that we have, and one of the big challenges moving forward, is that although that [the Natural History Study] has been a great resource to get a number people to do this study, we still want to capture more people. From the Natural History Study, we can probably identify about a hundred people total on the two ends, fifty people who are more severe and fifty people who are milder, who have typical disease-causing mutations but we know that there are a number of other people out there who had mutations who are so mild maybe they even have been recognized as Rett. So one of our big challenges is to tap into those groups of people and recruit then to do this study that I am describing now.

MC: So can you tell us since were able to also go outside Natural History Study and tap into other kids, I think it is going to be really important to figure out what are the criteria that we're going to be looking at, what symptoms are you looking at? So can you tell us a little bit about the type of individual that we're trying to find so that if someone watching says this says hey, that that sounds like my child? What are we looking for?

JN: It's a great question and a challenging one because we only have very broad strokes of what kind of things would look for. What I would say is that we want to find anybody who has a mutation MECP2, especially people who have a mutation in MECP2 who do not meet the clinical features of typical Rett Syndrome. There are a handful of these people and I think they're hard to identify because we had yet to identify real distinctive characteristics. Of the people that I do know of, they have a variety of social interaction abnormalities, some learning problems, and the degree of severity can be variable. We had some we had one child who really was very rather high functioning, had some obsessive-compulsive and attention issues, but actually had a relatively normal IQ. Whereas some of the other children had pretty severe autistic features and they spoke but only in very short sentences, but didn't have any hand problems. So I think we have to cast a broad net and it's hard for me to tell exactly clinically. The one thing I will say is that more and more girls who don't have the clinical features of Rett Syndrome for are getting tested for MECP2 mutations. So we're identifying more these people. So if those people ever show up, we would love to hear from them and try to enroll in this study.

MC: These might be kids who have language even though it's not at age level but who have language, who motorically, are in pretty good shape, who walk and run, who can climb the stairs, who have some hand function.

JN: All those things definitely

MC: Let's be broad and give you an opportunity to assess them and rule them in or rule them out.

JN: Yes.

MC: If I and others, through things like social media, get the word out and if parent says this could be my daughter what do they do? What should they do?

JN: A very easy thing to do is contact RSTR and I know that RSRT will definitely put them in touch with me. They can also directly call the Bluebird Clinic at Texas Childrens Hospital (the number is 832 822 7388).

MC: And ask to speak to you?

JN: Yes, they can leave their information. If they can't get in touch with me [directly], the office will get in touch, and I will get back to them.

MC: As you suggested, they can also contact me at RSRT and I can start to put some preliminary information together and pass it on to you. Do you think that you will have to see these kids in person or do you think with Skype and videos and talking to the parents you'll be able to get a clinical picture?

JN: I would love to see people in person but I understand the challenges of traveling and so I think we can try and work out things that can be done by phone calls, Skype, exchanging medical information and I think I can make a pretty decent assessments if they're not meeting the situation for Rett Syndrome.

MC: One of the aspects of this project that I found attractive is that all of the sequencing data and all of the phenotypic data will be deposited in a database, the national database for Autism research which is an NIH funded program, and will be available to the scientific community. I think is really valuable to share this information. Can you speak to that a little bit and also addressed what safeguards are put in place to protect the genetic information of individuals?

JN: Sharing genetic information amongst researchers is really critical because any one individual may not be able to really understand everything in genetics and I think that it's become the standard practice that genetic information is deposited into databases for other researchers to tap into, and for them may be explore it in ways that the primary search didn't think of in the first place. Now this does raise certain safety issues of privacy and concerns like that, but I'm we try and the NIH has devised a variety of methods to try to prohibit people using this information in ways that they shouldn't. This means using it in for discriminatory practices or denying insurance, and so really there are no names associated with any of the information that's placed there and although it's "a public databases", it's actually not just broadly available. You have to be approved researcher to be able to access the data and so there's a standardized process to go through to establish that you are really somebody who has a legitimate scientific

reason to look at the data. So there's no names, and the access is really restricted to legitimate scientific purposes.

MC: Now the concept of modifiers certainly is not unique to Rett Syndrome. This is a well-known genetic scenario that that happens probably in every disease, right? It helps to explain why some people are more severe/less severe, why they might do well with a certain drugs are not do well with another, why some people are susceptible to disease and not. So I just wanted to make that point.

JN: Yes, it's absolutely true. People have known for a while some of the things like certain susceptibility to bad side effects of drugs, certain genetic changes can predict if you're going to react badly to a drug, so that is really the beginning that this concept that we call personalized medicine where some people have genetic risks that are unique to themselves. Then you can look at their genetic composition and help guide their therapies. So in that situation, you can help decide if someone can be on a drug or not. More recently people have been pushing this idea of a modifier and really probably the best example was in cystic fibrosis where they were able to identify changes in gene that determine how likely it was that someone was going to get another infection, a bacterial infection. It really gave insight into the disease process that people didn't realize. It really will probably both help initially, it would help if you look at their genes and could say you're more at risk for getting this bacterial infection so we may need to change our therapies, but it also hopefully will provide insight into the pathology so you can modify the treatments for everyone to prevent these things. That's really where we wanted see a project like this go. What we hope is that we'll be able to find genetic modifiers of Rett Syndrome and not so we could predict if someone might be more severe or less severe, but really if we could find genetic changes that are protective, if we could understand what those genetic change are doing to the function of these proteins, then we might be able to mimic this with drugs and that's really where we want to go with this kind of project. We want to find things that will give us an insight to develop new therapies.

MC: When the proposal went to the peer review process, the reviewers were not shy about saying this is a rather high-risk proposal. In terms a building a resource for the scientific community, that's not high risk. This is going to be a database that hopefully will grow over time and will be a rich resource of information. Now whether will actually be able to identify modifiers is the risky piece. But I think that's where foundations like ours should fund riskier projects that might not be funded through more traditional agencies. Also, it's the kind of thing that we won't know until we do it.

JN: Absolutely, and I think you really hit the nail on the head there. You know, the NIH, by its very nature, is extraordinarily conservative and it really takes a foundation to say look we want to take a chance because we think this has a high reward and we're going to put some money in because hopefully that parlays into, like you said, a broader project that once you establish that it's working, you can seek outside funding. I think that this is a great way to parlay into larger

funding. But I think it is absolutely true; this is a risky project by the nature and like you said, the reviewers were not shy about that and I think we all understand that's the nature of it. I think the main point is that it is risky for us with the relatively small sample we have to discover modifier, but I think where there is low or no risk, is that we will have this banked information linked to clinical information that can be mined for a long time. So, what we say is the pure discovery, that just from this genetic information we will be able to find modifiers has a high degree of risk. However we know from the mouse work that there are modifiers and there are more genetic modifiers in mice that just need further refined or yet to be discovered. As we learn more those with the sequencing data available and publicly available to researchers, they'll be able to mine that database and determine if their favorite gene candidate is present in the human populations, if mutations in these genes are present, and that will really give a lot of strength to show that those animal work or those the ideas really pan out well because their existent in humans.

MC: So this is a project where we are really seeking partnership with the Rett community at large. We need your help. Dr. Neul has X number of patients within his natural history study but there's lots more individuals out there and if what we describe sounds reminiscent about your child, or a child that you may have met on somewhere along your Rett journey, then we really encourage you to contact me or contact Dr. Neul and let's determine whether your child may help us figure out how we might be able to help all Rett kids. So thank you very much Dr. Neul.

JN: One final thing I want to add to what you just said. I think the people we are extremely interested in are people who have MECP2 mutations but do not have Rett Syndrome. However we also very interested in the very high functioning people with Rett Syndrome. So people that really do have Rett Syndrome, but who maybe can speak in sentences and maybe can write some but they do really carry a true diagnosis of Rett Syndrome. We're definitely interested in those people too.

MC: Okay. Well, we wish you a lot of luck and we look forward to getting updates and sharing them with our community.