Q&A Males with Rett, MECP2 Mutations and Deletions  
Web Meeting 01/18/2018  
Speakers: Dr. S Skinner, Greenwood; Dr. A Percy, UAB; Dr. J Neul, Vanderbilt; Dr. S Kaminsky, Rettsyndrome.org; Paige Nues, Rettsyndrome.org; Jackie Ventura, Rettsyndrome.org; Ana McGrath, parent representative

**DIAGNOSIS**

What’s the difference between classical and atypical Rett? Which categories do our boys fit in?  
Many boys do not meet the clinical criteria for classical or typical Rett syndrome because they do not have a normal period of development. We generally believed that these boys do not meet criteria for any forms of Rett syndrome because of the lack of any regression, however we are learning that with careful exploration of more subtle historical features, a number of these boys do meet criteria for a form of atypical Rett. We are proposing that we term this “Male Rett Encephalopathy” because it is in general more severe than other forms of Rett syndrome.

Would a loss of skills be required for the new proposed classification?  
Yes. Regression with stabilization is a requirement for the diagnosis of any forms of Rett syndrome.

Difference in treatment for atypical and classical?  
There are no specific differences in the current standard of care for treatment. Treatment currently is entirely symptomatic, meaning that we guide therapies based on the symptoms. For example, if seizures are present we treat with standard anti-seizure medications.

How can we change the stigma about Rett for males with different mutations?  
If you mean that RTT does not occur in males, I would not call it a stigma as much as simply not understanding the actual occurrence. As discussed on the call, we have 30 males in the NHS with a large variation in severity. Based on subsequent information, a much large group of boys exists. These boys have not been characterized as those in the NHS. Doing this would be a great step forward in educating providers, companies, and others. Collecting more data regarding the spectrum of presentations seen in males with MECP2 changes and publishing and sharing that information is essential.
GENETICS

Advice on having another child since I am a carrier?
We recommend discussion with a genetic counselor. If you are a carrier, then the risk for each of your children to inherit the mutation is 50%. There are several options for reproductive planning and screening.

How can I find out what percent of my son's genes are affected?
Genetic testing will indicate which genes have mutations. In typical Rett syndrome in girls, in general only MECP2 mutations are present. Genetic testing will detect if there is a mutation in MECP2 though sometimes newer technology such as Next Generation Sequencing or other tests may be needed to detect low levels of mosaicism (mixture of normal and changed cells). This additional testing is not always routine and may require discussion with a clinician familiar with Rett syndrome and males with MECP2 mutations.

Will we be able to get genetic testing done during pregnancy like Downs syndrome?
Prenatal testing is available but requires amniocentesis or chorionic villus sampling (CVS), both of which are invasive. At this time it would not be recommended for all pregnancies (as is done in Down Syndrome), but can be an option in cases in which the chance of inheriting a MECP2 mutation is high, such as in the case where the mother is a known carrier. If a mutation is known in the family, the option of prenatal genetic testing is certainly an option and the risk and benefits should be discussed with a genetic counselor. If the mother is a known carrier of a mutation, then discussion with a genetic counselor about the options for prenatal testing should be discussed, but is an option.

NATURAL HISTORY STUDY

Many of the boys are too sick to make the trip to the Rett centers that participate in the Natural History Study. Is there a way that it can be done via Skype for these families?
We are exploring this option or other electronic mechanisms.

How do we become part of the Natural History Study? What to do if you live outside the United States?
Currently, NHS participation requires traveling to one of the enrolling sites, all of which are in the US. We have had a number of individuals make this trip and we have enrolled participants from a number of countries. We are exploring the option of enrolling people at a distance to capture at least some information.
RESEARCH

What is a Biomarker? And how do you make them better and receive better measures?
Biomarkers are things we can observe that are not symptoms of the disease, but might do things like predict that a person has the disease, how severely affected a person might be, that they will respond to treatment, or that they are responding positively to treatment before symptoms occur. These can be things like changes in the chemicals in the blood or changes in brain electrical activities. We are currently trying to identify such biomarkers in the NHS.

Rett clinics always say that treatment that works with girls will work for boys as well (including genetic therapy down the road). Is that true? If yes, what are the chances of any such treatment coming in our kids lifetimes?
We do not know this, but we generally believe it could be true. Ultimately we will have to try the treatments and see if it is true. Any approved treatment, regardless of the tested population could be utilized. It is very difficult to predict when these treatments will be available. We are seeing many exciting clinical trials being developed for initiation in the near future. We are witnessing recent exciting advancements in gene therapy in other disorders. Because of some of the challenges of applying these advances to Rett syndrome, it is difficult to predict how quickly these new advances will be applied to Rett syndrome. The Natural History Study continues to be a major source of data to support treatment advances.

What are the drugs in future trials that could help improve motor functions and cognition in our kiddos?
We do not know at this time, but this is something we are hoping will be the case in the therapies that are currently being explored in clinical trials.

If there are treatments that have reversed rett symptoms in mouse models, what is the roadblock in clinical trials?
Because of safety and technical challenges, we are not always able to manipulate genes in humans like we can in animals. The animal studies are important to show that Rett syndrome symptoms can be reversed and to point out potential treatment approaches to pursue. The animal work provided an idea of what we would like to do, but did not show us how to do it. In the time since that animal work many people have explored various approaches to try to reverse or modify the disease, and some of these
are either in clinical trials or being considered. It is a very technically difficult thing to do. The agent would still have to be tested in humans and in some cases, in higher animals such as non-human primates.

What is the future of genetic treatment for males? Is it going to be different than girls? Uncertain, but theoretically this could be something that might work. Gene therapy has many technical challenges that a number of groups are working to overcome. We would expect that the gene therapy protocol would be effective in males. It may be different from treatment in girls in terms of some technical issues.

What is the realistic time frame in obtaining a viable treatment/trial for our boys? It is always difficult to predict the future, and therapy development can be challenging and often takes longer than anyone would like. I do think that with increased recognition and understanding of this disorder, we can at minimum begin in the near future exploring what approved treatments would best help. We understand that the time-frame is frustratingly lengthy. It is for us as well. There are many technical and safety issues that make it very difficult to predict when a successful treatment will be available.

MEDICAL

My son has t158m which is associated with increased risk of seizures so what should be our top medical treatment priorities? We are only now starting to understand the clinical features of boys with MECP2 mutations, and we do not have a clear understanding of how different genetic mutations affect clinical symptoms. We only have a limited understanding of girls with Rett syndrome, and we have years of experience in that condition. In general, the relationship between specific mutations and clinical features holds true as a group, but not well for an individual. For this reason, we believe that any affected person should be monitored for common symptoms (like seizures) and treated when the symptoms occur. Knowing a specific mutation may help us share general information about the frequency of certain medical issues, but each child is a unique individual and may or may not exhibit all symptoms that other patients with the same mutation exhibit. There is no specific treatment based on the specific mutation. There is no treatment recommended prior to the onset of specific medical problems. It is helpful to be aware of certain risks for medical issues so screen and monitor for
the development of these conditions, but actual treatment will be based on which symptoms actually develop.

**Drugs that could help for respiration (apnea)?**
Breathing problems have been a major problem in all forms of Rett syndrome, and clearly are major issues in boys with MECP2 mutations. We have limited therapeutic options, however some of the drugs that are currently in clinical trials (sarizotan for instance) have show good effect in animal models to improve apnea, so we hope this will be true in people as well.

**When a child is reaching end of life, where do we begin? How can we ensure his experiences make a difference for others?**
This unfortunately is a challenging situation that seems to occur more in boys with MECP2 mutations than in girls with Rett syndrome. It is very important for the researchers to gather as much information about all affected boys, including those boys who are unfortunately at the end of life. Additionally, we have very little biological material from any affected boys, and few brain donations of boys. These human samples can be invaluable for science, and we would ask you to consider brain donation. We know this is a very difficult decision, especially in the situation of the trauma of having your child pass. For these reasons, it is best to start considering this in advance. Rettsyndrome.org supports these activities both financially and emotionally, and Paige Nues (pnues@rettsyndrome.org) is the person to contact to begin the discussion. Brains need to be harvested shortly after death, making this a very tight timeline.

In addition to end of life contributions, participating in the Natural History Study research and providing blood samples during various stages of life provide insights into the disease process.

**Other options for seizure treatment due to bone density issues?**
Nearly all seizures treatments (drugs, ketogenic diet) have the potential to affect bone density. One option to consider is vagal nerve stimulation. In general, I would say that the immediate risk of severe seizures outweighs the long-term concern of decreased bone density. It is helpful to have a close and good working relationship with your doctor in order to carefully manage seizure treatment, reconsidering the long term need for anti-seizure drugs in cases in which seizure frequency has declined or stopped.

**What are or even any current drugs that would help with motor or cognition?**
See above, currently we do not have any good approaches.
Please note that the following responses are those of Rettsyndrome.org, not our guest speakers:

**FUNDRAISING**

*Where do the funds go that are raised?*

We are glad that you asked! Two places: Funds raised are committed to Rett syndrome and MECP2 research that have the potential to benefit everyone touched by this devastating disorder, male and female. We are funding labs and researchers that are looking for today’s treatments and tomorrow’s “cure”. We actively support clinical trials that we believe will lead to treatments for both males and females. Rettsyndrome.org is also actively growing capacity and knowledge in clinics across the country to provide research and data collection channels for males and females, as well as avenues for improved medical care and treatments. Our support of the Natural History Study includes efforts directly related to enrollment of Males with MECP2 mutations and deletions. In addition, we use our funding to empower families by providing educational programming and connectivity to clinics and trials.

**MISCELLANEOUS**

*What is the difference between Rettsyndrome.org and RSRT?*

Rettsyndrome.org’s mission is to accelerate research that is leading to today’s treatments as well as tomorrow’s “cure”. We support groundbreaking research in 14 labs throughout the world, as well as clinical trials. We do this while empowering families with information, knowledge and connectivity. It would not be appropriate for Rettsyndrome.org to comment on the organizational activities of RSRT as we are not privy to their organizational goals, other than to say that they share our desire to eradicate Rett syndrome.