InterRett CONNECT

TELETHON KIDS INSTITUTE
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December 2015

NEWSLETTER OF THE AUSTRALIAN RETT SYNDROME STUDY

WELCOME

We would like to wish you all Seasons Greetings and a Happy New Year from Helen, Jenny, Nada, Amy, Barbara, Nan and Kingsley at the InterRett study. We would also like to wish you and your loved ones a safe, joyous, and relaxing festive season.

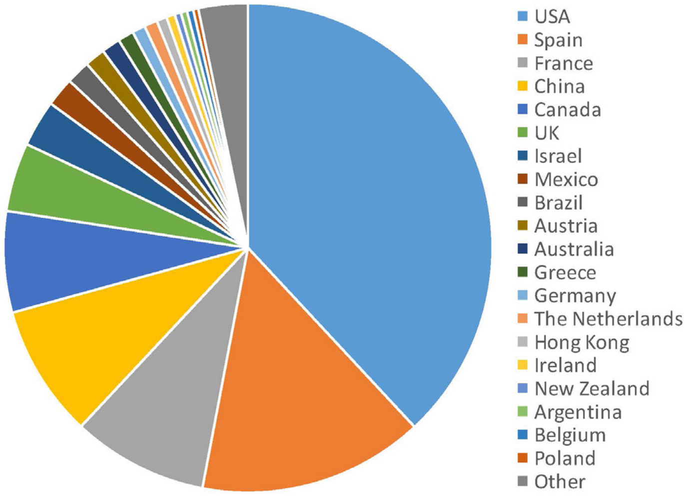
A Big Thank You!

We have many wonderful people to thank this year who have made the InterRett study possible. Thank you to the families of children and adults with Rett syndrome from around the globe for your ongoing support of our research through your participation in InterRett. We would like to thank members of the Parent Consumer Reference Group for their input and support of our work – we will continue meeting with this important group on a regular basis so that our work is informed by their experiences. If you are a parent who is interested in joining our meetings, then please email us at: Rett@telethonkids.org.au

In particular, we would like to acknowledge Rettsyndrome.org for their ongoing funding of this key global research initiative. We also want to thank the wonderful families and supporters who donate to Rettsyndrome.org so that funds are available to support vital research such as ours. We are all the more determined to make a difference for those affected by Rett syndrome.

INTERRETT CONTINUES TO GROW

With the wonderful contribution of families and clinicians around the world the InterRett database has continued to grow providing an increasingly powerful database for Rett syndrome research. Overall, since the inception of InterRett, data has been provided on over 2,600 girls and women with the largest proportions coming from the US, Spain, France, China, Canada and UK and. During 2015, the greatest numbers of family participants have been from China, the US and Brazil. Thank you to everybody, we very much value your time and effort.



Some countries are grouped as "Other" in the graph opposite because the numbers of participating families are very small but the countries are many. They include: Belarus, Bolivia, Bulgaria, Chile, Colombia, Costa Rica, Croatia, Cyprus, Denmark, Dominican Republic, Finland, Honduras, Hungary, India, Iran, Italy, Japan, Luxembourg, Macedonia, Malta, Norway, Peru, Portugal, Puerto Rico, Russia, Slovenia, South Africa, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates, Uruguay and Venezuela. It is truly wonderful to capture experiences around the world and we value all participation.

The InterRett family questionnaire is currently available online or as a paper version in English, Spanish, German, Italian, Mandarin, Dutch, Polish, French and Portuguese. We would like to continue translations into other languages.

CONFERENCE REPORTS

In May of this year Helen attended the **2015 IASSIDD Americas Regional Congress in Honolulu** where she had the opportunity to present on our Rett syndrome quality of life study as well as outcomes of different scoliosis management options. One particular highlight of this visit for her was the opportunity to meet with Michelle Lam and her daughter Brittany both of whom she had met eleven years previously at a Canadian Rett syndrome conference. Michelle and Brittany extended to Helen wonderful hospitality which was a highlight of her visit to Hawaii.

Helen and Brittany in Honolulu

In August Helen presented at the conference of the **Australian Association of Developmental Disability Medicine**: It's Alimentary, held at the Sydney Children's Hospital. The theme of the conference provided an ideal opportunity to present on "Feeding difficulties and growth problems in Rett syndrome and their management." The presentation was very well received and will also focus in an upcoming newsletter of the organization. Our gastrointestinal guidelines booklet is available on our InterRett website and can be freely downloaded at http://interrett.org.au/resources/guidelines,-reports-and-books/

At the end of October Helen was invited to speak at the **4th European Congress held in Rome** . In order to cater for families, therapists, educators and teachers as well as researchers and clinicians there were parallel streams running for most of the congress.

Helen in Rome

- The basic science stream included presentations from several top scientists from the US, Italy and Scotland. Topics included the repression of long genes by MECP2, the role of glial cells in Rett syndrome, the potential for gene therapy and for reactivation of the X chromosome.
- In the clinical stream, Helen talked about how our knowledge about Rett syndrome has changed over time and what we know about adulthood in Rett syndrome. Her talk was followed by presentations on transition, sleep and epilepsy. On the second day, a number of talks were given on breathing, heart and nutritional management in Rett syndrome. The Italian specialists frequently sourced their information from the clinical research papers published by our group.
- There were also sessions on Neuromotor Rehabilitation (Dr Meir Lotan from Israel spoke), Cognition and Communication, and Music Therapy. Helen gave a presentation highlighting Jenny's work developing new measures to assess gross motor function and evaluate walking activity.
- The final day included an update on the clinical trials currently in progress, where Dr Daniel Glaze spoke optimistically about the trial of NNZ-2566 (the drug now known as trofinetide), the next phase of which will again take place in the US. The results of some other trials were less positive. However, preliminary results from a French study investigating the use of bisphosphonate on bone density were promising.

Helen at Conference in Rome

The Congress audience was a mix of families, clinicians and researchers including laboratory based scientists. The families were predominantly Italian, and English/Italian translation was available for all sessions. There were also families from France, Belgium, the Netherlands and several Eastern European countries. We made available our guideline booklets and these disappeared like hotcakes! It was very gratifying for Helen to hear about the important role our Australian research outputs and publications are playing in Eastern European countries where there is little Rett syndrome expertise available.

RECENT RESEARCH

Our new sleep and breathing study

There has been little research investigating which girls and women with Rett syndrome may be at more risk of specific breathing issues. Similarly, research on sleep problems is relatively limited particularly in relation to what treatments may be effective. During 2015 we undertook a major project with English-speaking InterRett families living mainly in the US, Canada and the UK. We aimed to

- To identify how commonly specific breathing and sleep abnormalities are occurring in girls and women with Rett syndrome.
- To identify what may be risk factors and what may be protective factors for sleep and breathing problems in Rett syndrome.
- To find out whether there are treatments that are working for these conditions.

For the first time, we used a new web capture system called REDCap we invited families who had previously participated in InterRett, to fill out this questionnaire. To date we have contacted nearly 600 families and have had a very gratifying 80% response! We'd like here to express our heartfelt appreciation to all those families who have taken part.

At the moment we have preliminary results. We found that breathing irregularities such as hyperventilation and breath-holding affected girls and women of all ages and with most mutation types. However, the impact especially for breath-holding was worse for those with a p.Arg294* mutation, one of the generally milder mutations. We also found that respiratory infections, often involving hospital admission were common, but less likely to occur in those who were ambulant.

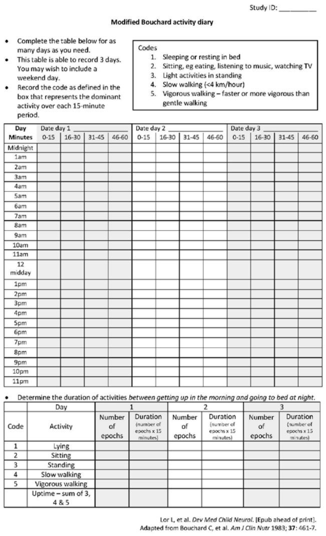
Concerning sleep, night-waking was common and was frequent for half the girls and women. Night laughing was less common than night-waking but was more frequently associated with some of the milder mutation types. Using standardized scales we also found that sleep problems were much more prevalent in Rett syndrome than in a normal control population. In particular, we found that those with Rett syndrome had particular problems with initiating and maintaining sleep and also excessive somnolence (falling asleep during the day). Once again we found relationships with genotype.

We are still collecting data and look forward to providing you with future results on the effectiveness of treatments both for breathing and sleep disorders. Please contact us at rett@telethonkids.org.au if you would like to participate. Finally we would like to thank and acknowledge our students, Jessica Mackay and Sharolin Boban who have both been working this project for their Honours degrees.

Uptime

Uptime is the time that a person spends weight bearing in standing and walking. The duration of uptime is associated with health benefits – natural stretch to muscles and tendons, the maintenance or improvement in muscle strength or fitness, and different perspectives by being up and about. We have recently modified a diary card measure for physical activity to measure uptime in Rett syndrome.

We found that the amount of uptime indicated the number of steps taken, particularly for those who could walk on their own. Measuring uptime therefore provides insights into physical activity and sedentary behaviour. Using our measure could facilitate the planning of suitable day activities and programs in response to your daughter's goals. We have made an assessment form that is available for you to download from our website at http://rett.telethonkids.org.au/media/1397275/Modified-Bouchard-activity-diary_Rett-syndrome_handout.pdf. Please share with your therapists and teachers who may want to measure your daughter's uptime and help to structure her day to increase her uptime.



Study ID: __________

Modified Bouchard activity diary

- Complete the table below for as many days as you need.
- This table is able to record 3 days. You may wish to include a weekend day.
- Record the code as defined in the box that represents the dominant activity over each 15-minute period.

Codes
1. Sleeping or resting in bed
2. Sitting, eg eating, listening to music, watching TV
3. Light activities in standing
4. Slow walking (<4 km/hour)
5. Vigorous walking – faster or more vigorous than gentle walking

Day	Date day 1 ________				Date day 2 ________				Date day 3 ________			
Minutes	0-15	16-30	31-45	46-60	0-15	16-30	31-45	46-60	0-15	16-30	31-45	46-60
Midnight												
1am												
2am												
3am												
4am												
5am												
6am												
7am												
8am												
9am												
10am												
11am												
12 midday												
1pm												
2pm												
3pm												
4pm												
5pm												
6pm												
7pm												
8pm												
9pm												
10pm												
11pm												

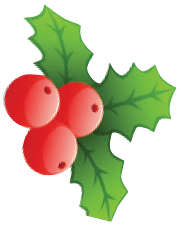
- Determine the duration of activities *between getting up in the morning and going to bed at night*.

	Day	1		2		3	
Code	Activity	Number of epochs	Duration (number of epochs x 15 minutes)	Number of epochs	Duration (number of epochs x 15 minutes)	Number of epochs	Duration (number of epochs x 15 minutes)
1	Lying						
2	Sitting						
3	Standing						
4	Slow walking						
5	Vigorous walking						
	Uptime – sum of 3, 4 & 5						

Lor L, et al. *Dev Med Child Neurol*. [Epub ahead of print].
Adapted from Bouchard C, et al. *Am J Clin Nutr* 1983; **37**: 461-7.

SHENZEN, CHINA

Jenny and Helen received funding in 2015 from Rettsyndrome.org to conduct a study that assesses early intervention for girls younger than six years old. There have been several studies that have shown that mice with a MECP2 mutation develop better motor skills if their environment is enriched, possibly due to the extra physical activity which then increases production of Brain Derived Neurotrophic Factor (BDNF). BDNF is an important protein for nerve cell growth and maturity. We need to examine carefully the precise benefits of intensive early intervention for children with Rett syndrome. This study involves a collaboration between Telethon Kids Institute and a team at the Rett Syndrome Comprehensive Research Institute in Shenzhen, China. We are just now starting to recruit for this study and we very much look forward to sharing our findings in our next newsletter.



DISORDERS RELATED TO RETT SYNDROME

International CDKL5 Disorder Database

The International CDKL5 Disorder Database is continuing to collect information. The aim is to collect information that is specific to this disorder from a larger number of families and their clinicians. This enhanced data repository will allow a more comprehensive profile of the clinical features that, in turn, will inform both clinical management and basic science research into cause and cure. All families with a child who has a mutation in the CDKL5 gene are invited to participate in this database. Please visit http://cdkl5.childhealthresearch.org.au/cdkl5_rego_new.php to register.

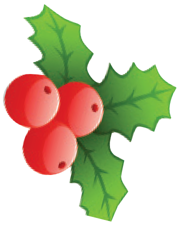
MECP2 Duplication Database

MECP2 duplication syndrome is a rare neurodevelopmental disorder that, in contrast to Rett syndrome, mostly affects boys. We have plans in the months ahead to develop a separate MECP2 duplication registry database. In the meantime we welcome families with a child with the MECP2 duplication syndrome to also participate in InterRett. For families of those with MECP2 Duplication or Rett syndrome who have not yet participated in InterRett please go to:
https://interrett.ichr.uwa.edu.au//irett_quest/registration/fam_registration.php

SEARCH OUR DATABASE

Please visit the graph generating tool on our website where you create graphs based on the information provided in the InterRett project by families and clinicians around the world. We welcome your feedback. The link is: https://interrett.ichr.uwa.edu.au//output/

For access to more of our research, please visit our website: http://www.interrett.org.au
You can find summaries of our recent research publications at: http://interrett.org.au/our-research/research-snapshots/
You can also follow our team on Facebook: http://www.facebook.com/interrett



2015 PUBLICATIONS ON RETT SYNDROME

The following papers written by members of the InterRett team have been published or accepted for publication in 2015. You can read snapshots of these papers on our website under 'Our Research', or copies of full papers can be obtained by emailing the team at Rett@telethonkids.org.au.

1. Epstein A, Leonard H, Davis E, Williams K, Reddihough D, Murphy N, Whitehouse A, Downs J. Conceptualizing a quality of life framework for girls with Rett syndrome, American Journal of Medical Genetics Part A (in press).
2. Downs J, Torode I, Wong K, Ellaway C, Elliott EJ, Christodoulou J, Jacoby P, Thomson MR, Izatt MT, Askin GN, McPhee BI, Bridge C, Cundy P, Leonard H. The natural history of scoliosis in females with Rett syndrome, Spine (in press).
3. Downs J, Torode I, Wong K, Ellaway C, Elliott EJ, Christodoulou J, Jacoby P, Thomson MR, Izatt MT, Askin GN, McPhee BI, Bridge C, Cundy P, Leonard H. Spinal fusion in early onset severe scoliosis improves survival in the child with Rett syndrome. Developmental Medicine and Child Neurology 2015 Dec 11. doi: 10.1111/dmcn.12984. [Epub ahead of print].
4. Urbanowicz A, Downs J, Girdler S, Ciccone N, Leonard H. An exploration of the use of eye gaze and gestures in females with Rett syndrome. Journal of Speech, Language and Hearing Research (in press).
5. Lor L, Hill K, Jacoby P, Leonard H, Downs J. A validation study of the Bouchard activity record that extends the concept of uptime to Rett syndrome. Developmental Medicine and Child Neurology. [Epub ahead of print].
6. Marr C, Leonard H, Torode I, Downs J. Spinal fusion in girls with Rett syndrome: postoperative recovery and family experiences. Child: Health, Care and Development. 2015 Mar 9. doi: 10.1111/cch.12243. [Epub ahead of print]
7. Jefferson A, Fyfe S, Downs J, Woodhead H, Jacoby P, Leonard H. Longitudinal bone mineral content and density in Rett syndrome and their contributing factors. Bone. 2015;74:191-8. doi: 10.1016/j.bone.2015.01.023.
8. Downs J, Leonard H, Jacoby P, Brisco L, Baikie G, Hill K. Rett syndrome: establishing a novel outcome measure for walking in an era of clinical trials for rare disorders, Disability and Rehabilitation 2015;37(21):1992-1996. doi: 10.3109/09638288.2014.993436
9. Downs J, Wong K, Ravikumara M, Ellaway C, Elliott E, Christodoulou J, Jacoby P, Leonard H. Experience of gastrostomy using a quality care framework: the example of Rett syndrome, Medicine 2014 Dec;93(28):e328. doi: 10.1097/MD.0000000000000328.
10. Urbanowicz A, Downs J, Girdler S, Ciccone N, Leonard H. Aspects of speech-language abilities are influenced by MECP2 mutation type in girls with Rett syndrome, American Journal of Medical Genetics Part A 2015;167(2):354-62. doi: 10.1002/ajmg.a.36871.
11. Wong K, Leonard H, Jacoby P, Ellaway C, Downs J. The trajectories of sleep disturbances in Rett syndrome. Journal of Sleep Research. 2015;24(2):223-33. doi: 10.1111/jsr.12240

Keep in touch with InterRett CONNECT

Every InterRett family helps to improve our knowledge and research into Rett syndrome. Please let us know if your contact details change. We don't want to lose you! If you would like to make a contribution to the next InterRett CONNECT, please contact:

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Email: Rett@telethonkids.org.au
Web: interrett.org.au
Mobile: 0419 956 946
Phone: 08 9489 7774/7790

We wish you a very happy and safe holiday period.