Joyeux Noël! 圣诞节快乐! Feliz Navidad! Wesołych Świąt! Frohe Weihnachten!

MERRY CHRISTMAS FROM INTERRETT!

InterRett

With the wonderful support of families around the world the InterRett project database continues to grow providing an increasingly powerful database for Rett syndrome research. The project is managed by the Australian Rett syndrome study team and has been funded by the International Rett Syndrome Foundation (IRSF, previously IRSA) since 2002.

Meet the Team

(from left): Janice Lim, Steph Fehr, Dr Jenny Downs, Alison Anderson, Medical Director Dr Helen Leonard and Ami Bebbington; Nada Murphy and Heidi Meyer (in absentia).

On behalf of the whole team we would like to ***thank you all*** for your valuable contribution to further research into Rett syndrome and CDKL5.

A special thank you from Nada…

"I have recently joined the InterRett team as a research assistant. I am a retired Clinical Psychologist and am enjoying the opportunities and challenges of this role. Previously I worked as a consultant in private practice in both child and adult fields and have extensive experience working with families. I worked with our local department for disabilities in the mid 1990's, and subsequently worked with people with disabilities and their families in a variety of roles until my retirement in 2006. Coming to work with InterRett has brought me back to work as a part time staff member which fits well with my various interests.

My work with the Australian Rett syndrome study team involves talking on the phone to families and entering data from our paper based questionnaires into the database. Some of you by now will be familiar with my very Australian accent; I know that it is not always easy to understand, thank you so much for persevering and working with me. With each call I learn more about Rett syndrome and am inspired by family stories of caring for a loved one with this condition.

So many people I have spoken to have given freely of their time with love, patience and dedication to help us with our research into Rett syndrome – *thank you.* There is something special about our modern world that allows one side of the world to work with the other side of the world to tackle the task of building our knowledge so that we can hopefully together make a real difference.

We understand that families may have difficulty in participating when faced with an unexpected crisis of one form or another. We are also mindful of how phone calls can intrude and we try our best to time calls so they might fit with family routine. Thank you all for your warm welcome when we do manage to connect. I look forward to talking to more families in the New Year."

Nada Murphy, Research Assistant.

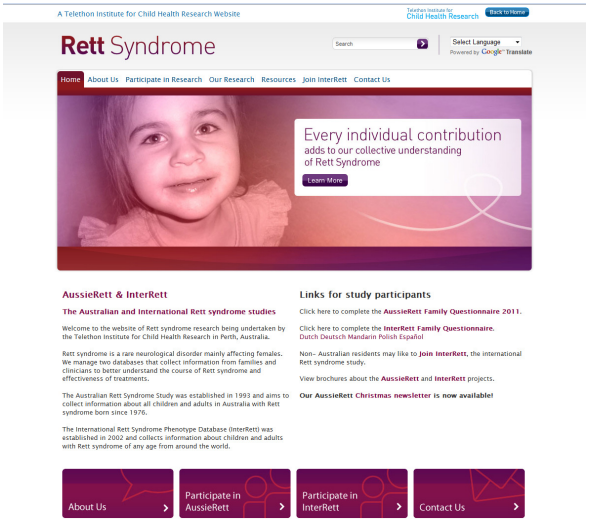
IRSF INTERNATIONAL RETT SYNDROME FOUNDATION

IRSF International Rett Syndrome Database – Telethon Institute for Child Health Research
PO Box 855 West Perth, Western Australia 6872, Tel:+61 8 9489 7790 Fax:+61 8 9489 700
Mobile:+61 419 956 946 Email: rett@ichr.uwa.edu.au Web: interrett.org.au

New website

In 2011 we launched our new website:

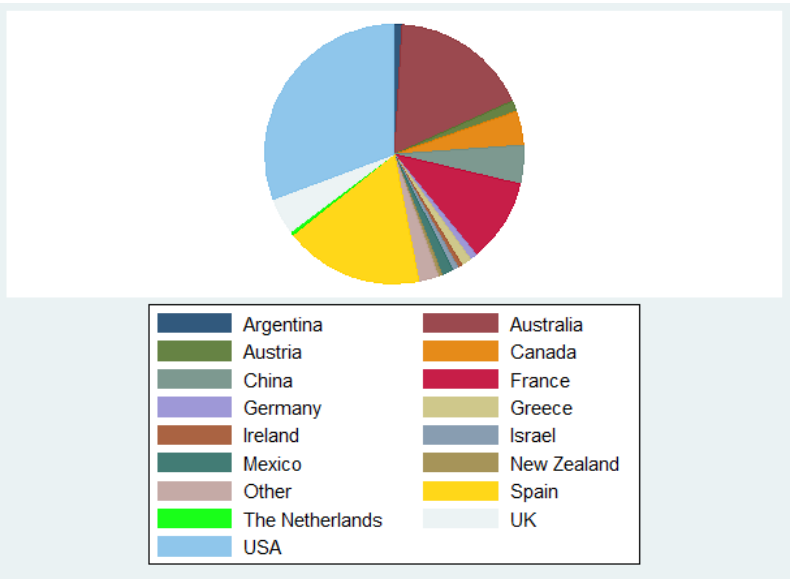
www.interrett.org.au and joined facebook!



The new website provides background information on both the InterRett and Australian (AussieRett) projects and the new *Research snapshots* section provides easy to read summaries of findings from our published research.

InterRett Widens its Multi-lingual Scope

The InterRett family questionnaire is now available in online or paper version in English, Spanish, German, Italian, Mandarin, Dutch, Polish and French. It has recently been translated into Hungarian and will be available in this language in early 2012. We are very grateful to those who have generously given their time to help with the important task of translating. This has contributed greatly to the diverse spread of families involved worldwide as shown in the graph.



The *Other* category includes countries with less than 10 cases in the database: Belgium, Bolivia, Brazil, Bulgaria, Chile, Colombia, Costa Rica, Cyprus, Denmark, Finland, Honduras, India, Iran, Italy, Japan, Luxemburg, Macedonia, Malta, The Netherlands, Norway, Peru, Poland, Portugal, Puerto Rica, Slovenia, South Africa, Sweden, Switzerland, Taiwan, Turkey, United Arab Emirates and Uruguay.

New Studies

International CDKL5 Disorder Register

We are very excited to announce that we are developing a new International CDKL5 Disorder Register!

The CDKL5 disorder is caused by mutations within the CDKL5 gene. There appears to be much variability in the presentation of males and females with this disorder, with some families receiving a diagnosis of the early-onset seizure form of Rett syndrome and others a diagnosis of infantile spasms or West syndrome.

We are implementing the new register to help answer the many questions still surrounding the CDKL5 disorder. The overall aim of this project is to collect information from families and their clinicians about their son or daughter with the CDKL5 disorder. The first consumer reference group teleconference was undertaken earlier this month with families located in Australia, USA, UK and Ireland. The specific CDKL5 family questionnaire for families will be ready for completion in the first half of 2012 and a second follow-up questionnaire will be distributed in 2013. If you would like more information please contact cdkl5@ichr.uwa.edu.au.

IRSF INTERNATIONAL RETT SYNDROME FOUNDATION

IRSF International Rett Syndrome Database – Telethon Institute for Child Health Research
PO Box 855 West Perth, Western Australia 6872, Tel:+61 8 9489 7790 Fax:+61 8 9489 700
Mobile:+61 419 956 946 Email: rett@ichr.uwa.edu.au Web: interrett.org.au

Early development study

Joanne Lee's Masters of Clinical Psychology project will be a more detailed description of early development and regression for girls with Rett syndrome. Joanne has been interviewing mothers of young girls in both the InterRett and AussieRett studies to find out more about this period of time in their daughter's lives. Joanne would like to give a special Thank you to those who have participated and looks forward to talking to more families in the New Year.

Epilepsy study

Epilepsy is a common issue with children with Rett syndrome and research has shown that its occurrence may be associated with certain mutations on the *MECP2* gene. It is also found that epilepsy in Rett syndrome can be difficult to manage and resistance to mainstay anti-epileptic treatment is common. Using information provided by InterRett, we will examine the influence of mutation type on the onset, presence and severity of epilepsy, and the relationship between use of different anti-epileptic medications and seizure control. This study will provide better insight into poorly controlled epilepsy.

Research using InterRett data

Bebbington, A, Downs, J, Percy, A, Pineda, M, Ben Zeev, B, Bahi-Buisson, N, Leonard, H. The phenotype associated with a large deletion on *MECP2*. European Journal of Human Genetics. In press.

Background

Large deletions in the *MECP2* gene have been identified in many individuals clinically diagnosed with Rett syndrome. The InterRett database contains information on individuals with a wide range of mutations including large deletions.

What we did

We described the clinical outcomes of a group of 51 individuals who had a large deletion mutation of the *MECP2* gene. We compared health outcomes in this group with those individuals in the InterRett and AussieRett databases with other mutation types. We also presented two cases studies describing the clinical history of two individuals with a large deletion spanning sections of exons 3 and 4.

What we found

The health outcomes of those with a large deletion varied considerably, even in those with very similar deletions. As a group those with large mutations were observed to present at an earlier age with symptoms such as epilepsy, scoliosis and breathing abnormalities in comparison to the group of individuals with a different mutation type. Conversely, those with a large deletion were less likely than those with other mutations to have air swallowing or kyphosis (a form of spinal curvature) symptoms.

What does it mean

The function of the *MECP2* gene is influenced by several other genetic factors. Individual differences in these factors likely explain the variations in symptoms observed across individuals with a large deletion. Our study provides an overall profile of the clinical picture in those affected with a large deletion that can assist with family counselling and inform management of their care.

Fehr S, Bebbington A, Ellaway C, Rowe P, Leonard H and Downs J. Altered attainment of developmental milestones influences the age of diagnosis of Rett syndrome. Journal of Child Neurology. 2011;26(8):980-7.

Background

Regression, including the loss of previously learned skills, such as hand function and communication skills, is one of the most suggestive features of Rett syndrome. These symptoms often first appear when the child is about 18 months of age. However early development of the girls prior to this age can be variable.

What we did

We examined the patterns of achieving motor and communication milestones in 293 girls whose parents provided information to the Australian Rett Syndrome Database and the International Phenotype Database, InterRett. We then examined how this pattern related to other factors such as the age at regression, age at diagnosis and *MECP2* mutation.

What we found

We found that most girls learned to sit by 10 months of age, were able to either babble or use words, and approximately half learned to walk. About half the girls began to regress at about 18 months and many parents expressed concerns about unusual behaviours or development during infancy. Parents often commented that their daughter was “floppy”, excessively quiet or placid or had delayed crawling.

Girls with the p.R133C, p.R306C or p.R294X mutations were more likely to achieve developmental milestones with the majority learning to sit, walk and either babble or use words. Girls who had the p.R133C mutation or C-terminal deletions also tended to regress at a later age than those with other mutations.

Girls who were able to walk unassisted and able use words were diagnosed at a later age. Those who had achieved fewer milestones tended to be diagnosed earlier. Girls with C-terminal deletions, large deletions, p.R133C, p.R294X or p.R306C mutations were diagnosed later than those with the p.R255X mutation.

What does it mean

Our findings suggest that early development in girls with Rett syndrome was often atypical. Many parents felt that their child had displayed unusual behaviours or development during infancy and was often described as overly calm, placid and/or ‘‘floppy”. As they became older, some parents were also concerned about their child’s difficulties in rolling, crawling, or pulling to stand.

Our findings also suggest that these patterns of early development often precede the appearance of other symptoms more characteristic of Rett syndrome. Even though these patterns are not specific to Rett syndrome, their presence should not delay confirmation by *MECP2* testing if other criteria for Rett syndrome are met.

Fehr S, Downs J, Bebbington A, Leonard H. Atypical presentations and specific genotypes are associated with a delay in diagnosis in females with Rett syndrome. American Journal of Medical Genetics Part A, 2010. 152A: 2535-2542.

Background

There is often a delay between the time when the symptoms of Rett syndrome first appear and when a diagnosis of Rett syndrome is made. We investigated the factors that may affect the age at diagnosis for girls and woman with Rett syndrome.

What we did

Using information from 909 families participating in the Australian Rett Syndrome Study and InterRett, we investigated whether the age of the child's diagnosis was related to the familiy's socioeconomic status, the child's birth order, mother's age and the age when typical Rett syndrome features first appear.

What we found

We found that girls who develop symptoms that are typical of Rett syndrome were diagnosed at an earlier age. Therefore those who lost hand function or communication skills later or who developed hand stereotypies at an older age were diagnosed later. Girls with the p.R133C or p.R294X *MECP2* mutations also tended to have a later age of diagnosis. The families' socioeconomic status was not related to the age at diagnosis for Australian families. However for families participating in the InterRett database, a younger age of diagnosis was associated with higher levels of parental education or occupation.

What does it mean

There is a broader range of symptoms in Rett syndrome then just those which follow the classical picture. These include the milder, less typical presentations which sometimes involve a delayed onset of regression or a delayed occurrence of hand stereotypies. It is important that clinicians are aware of these presentations so that diagnoses are not missed as has previously occurred. We need to make sure that doctors are aware of the full extent of the clinical variability of presentations in Rett syndrome.

Lim, F, Downs, J, Li, J, Bao, X, Leonard, H.Barriers to Diagnosis of a Rare Neurological Disorder in China—Lived Experiences of Rett Syndrome Families. American Journal of Medical Genetics Part A. 2011; online.

Background

The InterRett study continues to explore opportunities for collaborative work afforded by our long-standing relationship with Professor Xin-Hua Bao and colleagues at Peking University First Hospital. During 2011, honours student, Janice Lim obtained support from our Chinese colleagues together with Jianghong Li (Curtin University and Telethon Institute for Child Health Research in Western Australia) to conduct a study to investigate the experience of Chinese families in obtaining a diagnosis of Rett syndrome.

What we did

Janice, who speaks fluent Mandarin, discussed the process of diagnosis of Rett syndrome with 14 families who are participants in the InterRett project and live in different regions of China. She transcribed and summarised the family reports and wrote a paper describing her findings. The paper is titled "Barriers to

diagnosis of a rare neurological disorder in China – lived experiences of Rett syndrome families" and was recently published in the scientific literature.

What we found

Chinese families experienced considerable delays in diagnosis involving visits to multiple health professionals. There were frustrations with the health care system with parents encountering long waiting lists, high costs in having to travel to receive specialist care and short consultation times. Families were also concerned about the lack of information about Rett syndrome and its management available in China.

What does it mean

Diagnosis of Rett syndrome can be challenging for both families and clinicians in any country but those living in developing countries face additional obstacles such as hospitals and health care systems that are over-burdened and a lack of local diagnostic expertise. In China, as in other countries, a diagnosis is important to families for future planning and management of care for their family member with the condition. There is a need for strategies to disseminate knowledge on both diagnosis and management throughout the country together with the establishment of genetic testing systems to support the clinical diagnostic process.

What the future holds for InterRett

The InterRett project is about to enter its 10th year! While we continue to make every effort to promote the project and increase participation our main focus is now the translation of this information into knowledge that can assist clinicians and families. We are increasingly exploring ways in which we can analyse these data to address the many questions that remain unanswered. As in the past, we will reach out to the global Rett syndrome research community and invite others to work collaboratively with us in achieving this goal.

PLEASE HELP us to continue our research by:

⇒ Completing your Family Questionnaire

⇒ Sending us any new or updated genetic information on your child

⇒ Encouraging your child's doctor to complete the Clinician Questionnaire

⇒ Passing on our details to other families with a child with Rett syndrome

For more information go to interrett.org.au

IRSF INTERNATIONAL RETT SYNDROME FOUNDATION

IRSF International Rett Syndrome Database – Telethon Institute for Child Health Research
PO Box 855 West Perth, Western Australia 6872, Tel:+61 8 9489 7790 Fax:+61 8 9489 700
Mobile:+61 419 956 946 Email: rett@ichr.uwa.edu.au Web: interrett.org.au