The Australian


Rett Syndrome *Study*



Inaugural report

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Telethon Institute for Child Health Research

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Foreword

By Dr Helen Leonard

It is with much pleasure that we publish the first Report of the Australian Rett Syndrome Study, which is based in Perth, Western Australia at the Telethon Institute for Child Health Research.

This report marks the inaugural presentation of our activities to parents and others who follow this research. In this report we outline the studies carried out to date as well as the publications and presentations that have been derived from this research. Our appreciation goes to the Health Department of Western Australia for their sponsorship of this publication. In addition, we would like to thank Pam Holmes for her work in producing this report.

The continuation of the project is only possible with the involvement of many contributors. Families have spent many hours completing surveys which have provided excellent data. We also appreciate the time and dedication of clinicians who have notified cases to our study and provided us with valuable clinical information. We warmly thank all the families and clinicians for their ongoing support and contribution to the project.

We would also like to acknowledge Mr Bill Callaghan and Mrs Janelle Lillis for their ongoing support for our work.

Regards

Dr Helen Leonard

Foreword

By Mr Bill Callaghan

Rett syndrome is a severe disorder which is multi-faceted in the symptoms it presents.

The condition demands investigation by skilled scientific researchers who are committed to such a task. Fortunately, in Australia, this situation has existed since 1993 in the form of The Australian Rett Syndrome Study.

Led by its Co-ordinator, Dr Helen Leonard, the Study has been marked by a diversity of topics as is evidenced in this publication. Importantly, throughout its lifetime, the Study has actively sought and received the support of Australian Rett syndrome families. That relationship between researcher and family has been further enhanced by this Report because, among other things, it seeks to inform the group who supplied the information for analysis, namely, the Rett syndrome family.

The Australian Rett Syndrome Study, of which this Report is a significant part, has made, and continues to make, a vital contribution to the knowledge of Rett syndrome, both in Australia and internationally.

Regards

Mr Bill Callaghan
President

Rett Syndrome Association of Australia

Introduction

introduction

The Australian Rett Syndrome Study is based at the Telethon Institute for Child Health Research located in Subiaco, Western Australia. The Institute is a world-class centre for child health research. Areas of research include asthma, infectious diseases and cancer as well as birth defects and childhood disabilities.

The Australian Rett Syndrome Study was established in 1993 and operates in collaboration with a number of organisations and research centres: Princess Margaret Hospital for Children, Children's Hospital at Westmead (Sydney), Disability Services Commission, Royal Perth Hospital and Curtin University.

The original impetus for this study was the lack of information on the frequency of this condition. Whilst isolated cases were being uncovered around the nation doctors were not able to answer the question 'How common is Rett syndrome in Australia?'. In addition, there was little information relating both to the patterns of features in this disorder and the long-term prognosis for the child newly diagnosed with Rett syndrome. This information is highly valued by both parents and health professionals.

Over the past few years, a central focus of our study has been to collect data about Rett syndrome in Australia so that in future, parents can be provided with up-to-date and accurate information about the progression of the disorder, the variability in its severity and the best ways of managing the care of children and women with Rett syndrome.

Staff working on the Rett Syndrome Study

Telethon Institute for Child Health Research

Introduction

introduction

Here at the Australian Rett Syndrome Study our broad aims are:

- to monitor patterns of Rett syndrome occurrence
- to develop an ongoing data collection which will provide information about:
    - the impact of Rett syndrome on functioning, daily living activities & health
    - the impact of Rett syndrome on families
    - the types of medical and therapeutic interventions
    - the adequacy and quality of treatments and services provided
- to provide a population data source for genetic research which is a model for use elsewhere in the world
- to share information with medical, educational, and health professionals to increase understanding about Rett syndrome
- to make available to families of newly diagnosed girls information that provides them with some expectations about their daughter's future.

A unique feature of our study is that it involves almost all families in Australia who have a daughter with Rett syndrome born since 1976. This is in contrast to many studies overseas where only selected groups of children are involved. Being 'population-based' allows us to be confident that our research findings will be applicable to all girls with Rett syndrome.

Here in Western Australia we also provide opportunities for parents to meet and share experiences through education evenings and social functions. Another important element of our study is providing information to interested community members, health professionals and other groups, such as special education teachers and therapists.

Members of the study team with one of the study participants

Introduction

What is Rett syndrome?

Rett syndrome is a relatively rare but serious neurological disorder generally affecting girls. However, in recent years boys have also occasionally been diagnosed.

In most cases, the baby girl with Rett syndrome appears to develop normally.

However, some time in the first 6 to 18 months of life, this normal pattern of childhood development does not progress.

In most cases there is a loss of communication and hand skills and the development of unusual hand movements.

During this time the child may display autistic features and appear agitated and distressed.

In the long term, most children are no longer able to talk and many find it difficult or are unable to walk.

Other clinical features include poor head growth, epileptic fits, spinal curvature, abnormal breathing patterns, gastrointestinal and sleeping problems.

Therefore Rett syndrome is usually associated with severe intellectual and physical disability and often with considerable health problems. However, despite this many parents remark that over time girls may appear to improve in their social awareness and communication skills.

Introduction

Clinical features & diagnosis

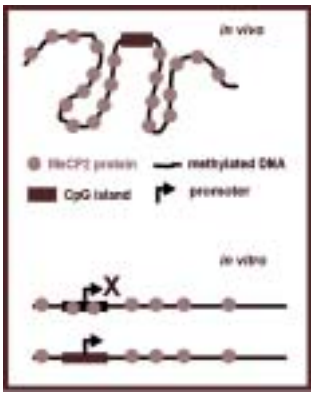
Until recently the clinical diagnosis of Rett syndrome was generally made when certain physical and behavioural features were present and after tests to exclude other disorders had been carried out.

- Girls in whom all the features were present were considered to have **classical** Rett syndrome.
- Girls with most, but not all, of the features were considered to have **atypical** Rett syndrome.

The clinical diagnosis has often been uncertain in early childhood as the symptoms may be confused with those occurring in other disorders such as autism, cerebral palsy and global developmental delay. However, since the discovery of the gene responsible for Rett syndrome the clinical diagnosis may often now be confirmed by a blood test.

Genetics of Rett Syndrome

In 1999, a genetic breakthrough occurred in the laboratory of Dr Huda Zoghbi in Texas, USA.



Rett syndrome was found to be associated with an abnormality in the *MECP2* gene (pronounced "meck-p-two") which is located on the X chromosome.

The *MECP2* gene is an extremely important and interesting gene for scientists. It is thought to play an essential role in development in the crucial early years of life.

At certain times during development some genes need to be switched on and at other times switched off.

The *MECP2* gene is involved in switching off other genes.

However, because there are abnormalities in this gene in Rett syndrome it is thought that it fails to switch off specific genes which should be switched off. Consequently normal development may be altered.

Over the past two years much effort has been directed towards genetic research in many centres world-wide.

North America	Europe	Australasia	Other countries
· USA	· France	· Australia	· Israel
· Canada	· Wales	· New Zealand	
	· Denmark	· China	
	· Scotland	· Japan	
	· Sweden		
	· Spain		
	· Italy		
	· Germany		

Process of the Study

The Australian Rett Syndrome Study is unique in that it is population-based, that is, it includes almost all girls with the disorder in one country. In order to identify all girls with Rett syndrome in Australia we have used a variety of methods and been assisted by two particular organisations:

- the Rett Syndrome Association of Australia (RSAA)
- the Australian Paediatric Surveillance Unit (APSU)

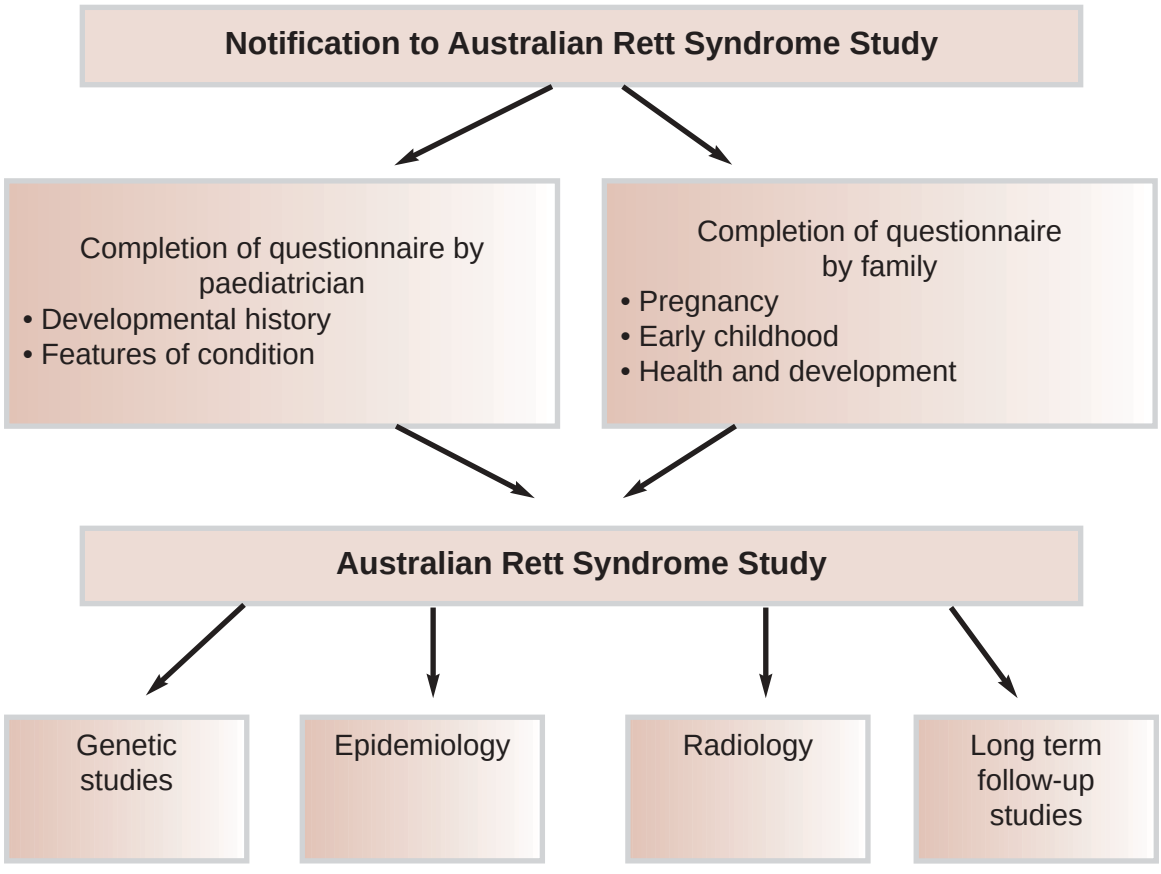
The Rett Syndrome Association of Australia (RSAA) is a support group for parents and carers of girls and women with Rett syndrome. Referrals to this support association come from doctors, teachers and other parents (www.rett.uwa.edu.au/state/html).

The purpose of this organisation is threefold:

- to develop an understanding and awareness of the condition;
- to assist, where possible, the advancement of study, research, therapy and care; and,
- to support families and carers in coping with the disorder.

The Australian Paediatric Surveillance Unit (APSU) was set up in 1993 to facilitate research into rare childhood conditions. The APSU is in contact with paediatricians Australia-wide who may come into contact with these families. The APSU liaises with paediatricians and then notifies our study when a new case of Rett syndrome is reported.

In addition, we liaise closely with specific groups of children's specialists nationwide such as neurologists and geneticists. We also attend and present our research findings at their specialist meetings and conferences to ensure that they have access to our latest research findings.

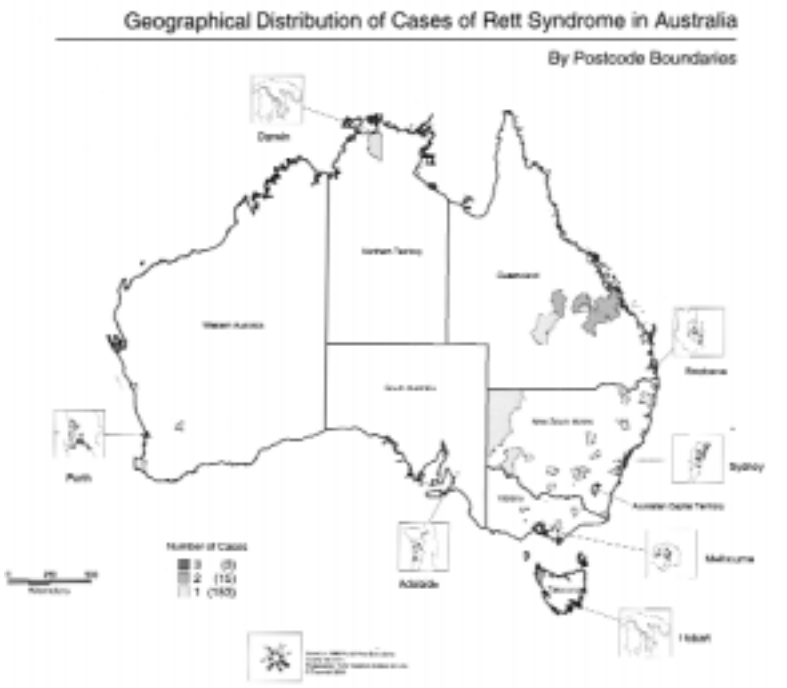


Epidemiology

epidemiology

• The first aim of the epidemiological component of the study was to answer the question *"How common is Rett syndrome in Australia?"*. It is important to know how common such a condition is so that planning for the provision of services for these children and adults can be made.

During 1993 and 1994 a group of 134 Australian girls aged less than 18 years was enrolled in the study. This allowed us to estimate that 1:10,000 girls or approximately 12 girls per year would be diagnosed by the age of 12 years in Australia.

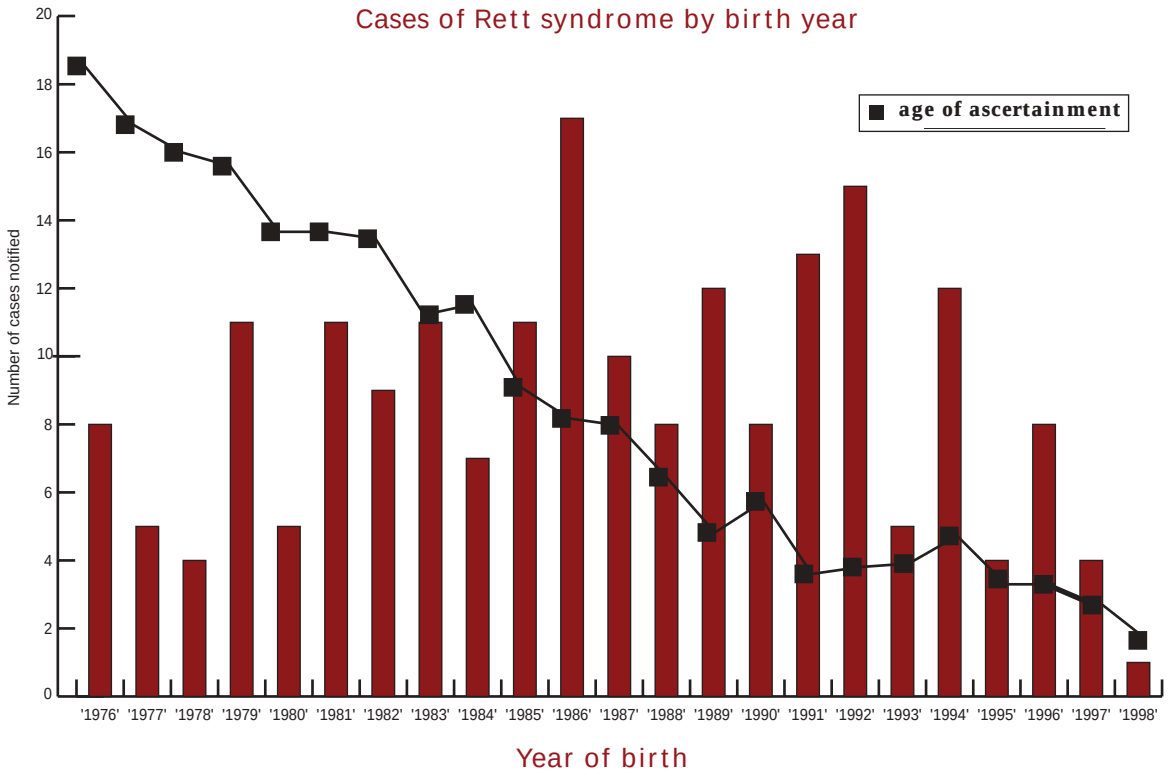


• The second aim was to provide a total population of cases that could be followed in order to observe the changes in functioning and health that occur over time in Rett syndrome. Since 1993, we have continued to enrol new families. The graph on the following page shows the number of cases notified to the study since its inception in 1993. The decreasing age of ascertainment reflects the increasing awareness of Rett syndrome in the medical community. The recent availability of a genetic test has also allowed for a definitive diagnosis at an earlier age.

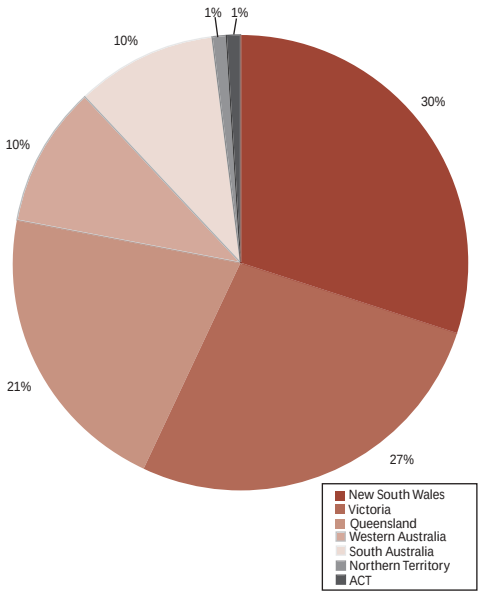
Epidemiology

By July 2000, (at the beginning of the first formal follow-up study) 199 girls and women in whom Rett syndrome had been confirmed according to the study definition had been reported to the study.

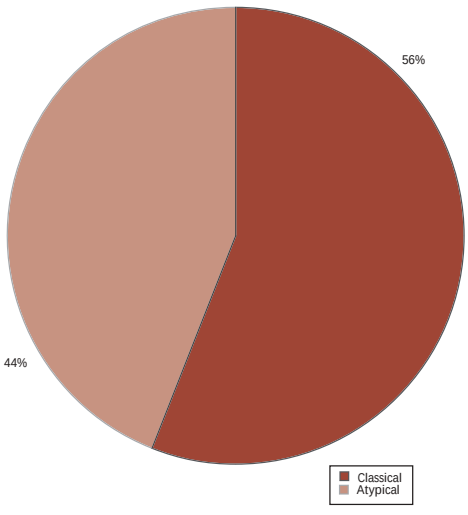
By December 31st 2001 a total of 227 girls and women meeting our study definition of classical or atypical Rett syndrome had been reported. Fourteen of these girls had died.



State of Residence of girls and women with Rett syndrome



Rett syndrome cases: classical and atypical



Genetic Studies in Australia

Since the discovery of the association between abnormalities in the *MECP2* gene and Rett syndrome, we have had in Australia a unique and unprecedented opportunity to study genotype-phenotype correlations. In other words, we are in the position to be able to investigate whether there is a relationship between specific mutations and the severity of clinical features in Rett syndrome.

There would appear to be some variation in the functioning and health of girls and women with Rett syndrome. Understanding the link between the gene mutation and the presentation of Rett syndrome will give parents and doctors a better 'prediction' about development and the potential health conditions which may occur in an individual child. This information will be of use both to families and doctors at the time of diagnosis and to doctors in the planning of the long-term management of their patients.

The *MECP2* gene is on the X chromosome. X inactivation is a genetic mechanism by which females who have two X chromosomes 'silence' one of their two active X chromosomes. There is some evidence that in girls and women with Rett syndrome, this 'inactivation' may not always be random and may be 'skewed' more often than expected. We wish to identify whether this influences how a girl or woman may be affected by particular genetic mutations.

Dr Huda Zoghbi and her first Rett syndrome family at the announcement of the discovery of the gene for Rett Syndrome

These genetic studies will enable us to learn more about the nature and spectrum of Rett syndrome. They will have important implications for clinical practice and it is hoped that they will provide new opportunities to develop more effective interventions in Rett syndrome. In Australia genetic testing is being carried out at the Children's Hospital, Westmead, Sydney and at the Neurogenetics laboratory at Royal Perth Hospital, Perth.

At the end of 2001:

• Genetic testing for mutations had been carried out on over three-quarters of girls and young women in our study.

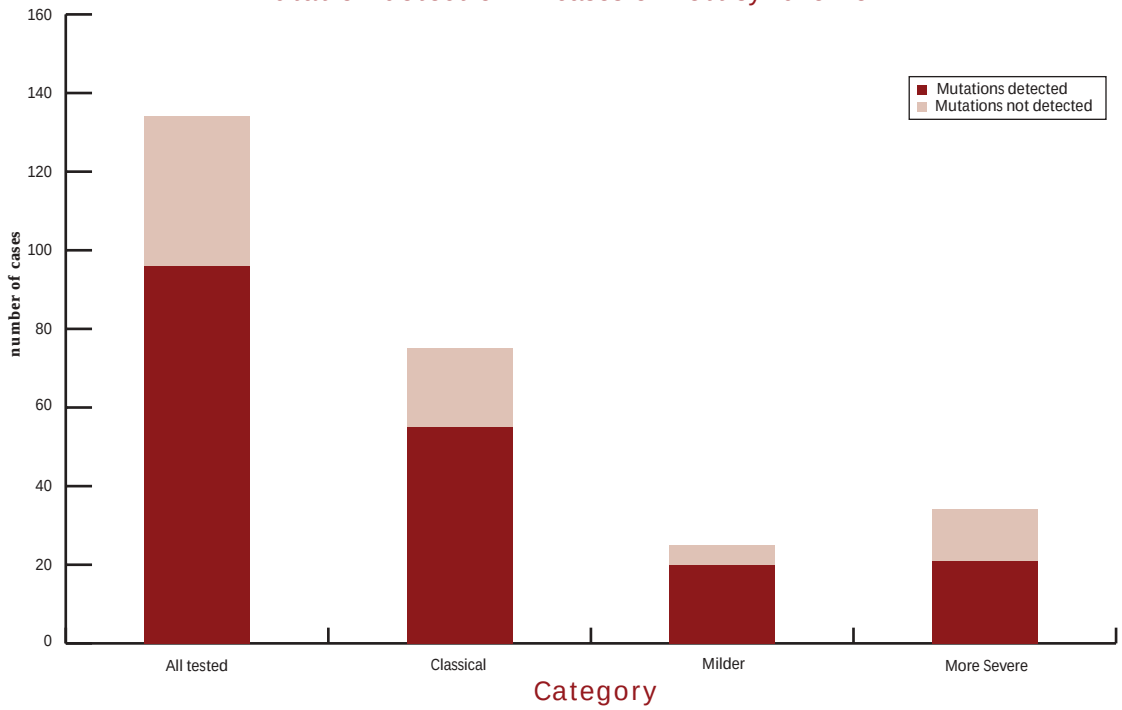
• X inactivation studies as well as mutation screening had been completed on a third of cases in the study.

How common are mutations in Rett syndrome in Australia?

• Mutations have been identified in 70% of cases overall but more commonly in classical (73%) than atypical (65%) cases.

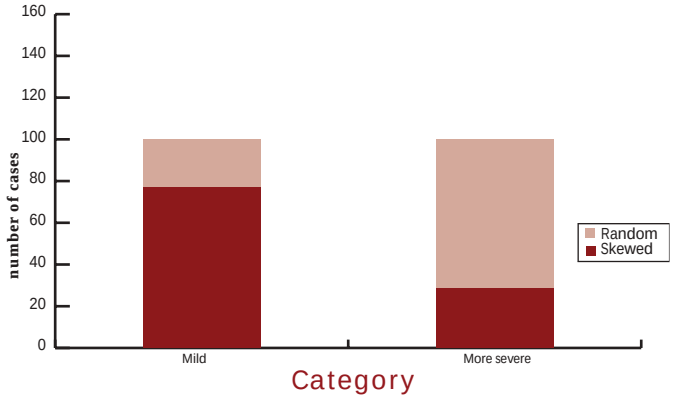
• In about one third of cases no mutation has been detected at this point in time. As the screening technologies improve we will be searching for mutations in other regions of the gene.

Mutation detection in cases of Rett syndrome



• Skewing of X inactivation was identified in 43% of cases with a mutation but also in a similar proportion of the cases who do not have a mutation. The preferential silencing of one of the X chromosomes (that is skewed X inactivation) may be favourable or harmful. For example, if the X chromosome carrying the abnormality is silenced more often than not then the outcome of disease may be more favourable. The amount of skewing may in part explain the reason why two girls with an identical mutation present with a different severity of Rett syndrome.

X inactivation in Rett syndrome cases



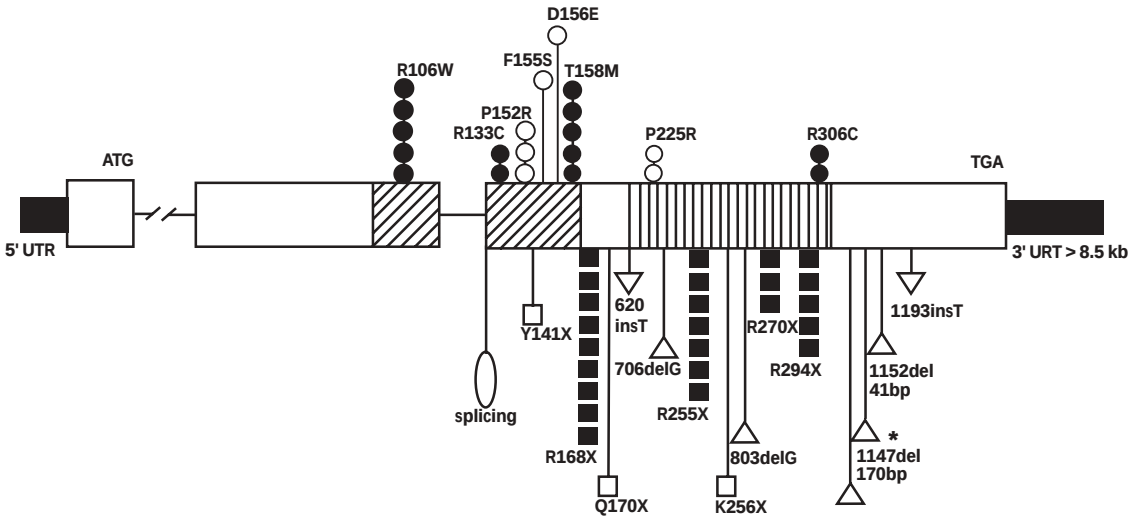
This shows that skewing is much more common in milder cases than in those with severe or early onset Rett syndrome.

• Worldwide, nearly 200 different *MECP2* pathogenic mutations have now been identified.

• In our study thirty-four different pathogenic mutations were identified with 20 of them each affecting only one individual. In other words, there are about 14 common mutations in the Australian group.

• The most common mutation in our study was the T158M, a missense mutation occurring in the methyl binding domain, accounting for 15% of mutations. On a worldwide scale this is also one of the most common mutations along with the R168X nonsense mutation.

• In 79% of cases in our study three or more individuals were affected by the same mutation.



Amir et al 2000

MECP2 mutations are also now being found in individuals who do not appear to have Rett syndrome, for example in infants who have neurological problems at birth, in childhood schizophrenia and in other developmental disorders such as autism and familial intellectual disability. One of the many challenges now is to further explore the role of the MECP2 gene in these other neurodevelopmental disorders.

X-Ray Studies

In 1996 we conducted a study to investigate hand and foot bone abnormalities in Rett syndrome. At that time, there was no diagnostic test, physical marker or distinctive features that could confirm Rett syndrome. Finding a bony abnormality characteristic of Rett syndrome could potentially aid with diagnosis.

• Hand and foot X-rays of 94 girls with Rett syndrome were compared with X-rays of girls of the same age obtained from hospital X-ray libraries in Perth.

• At the same time, we also asked parents to complete a dietary questionnaire to allow us to assess calcium intake.

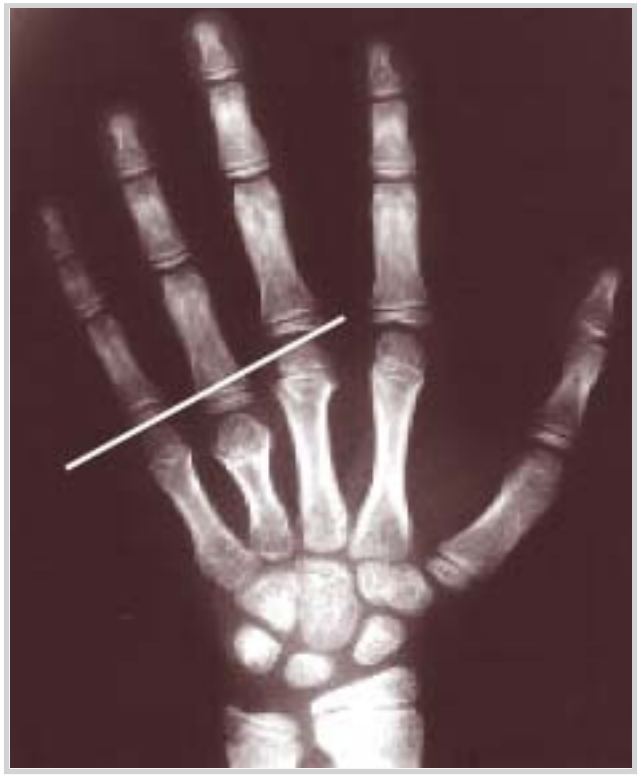
In reviewing the X-rays and comparing them with girls without Rett syndrome, we found that:

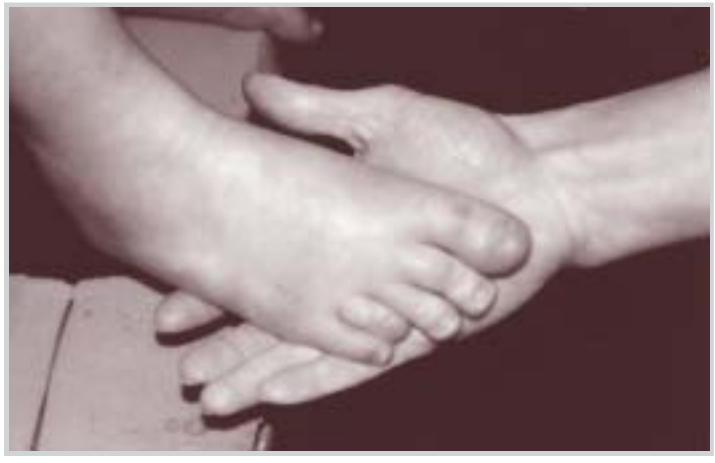
• A short fourth toe (metatarsal) or a short bone in the arm (ulna) was present in at least half of girls aged five years and over with Rett syndrome.

• Both these features were much more common than in the X-rays of girls who did not have Rett syndrome.

• Shortening of the fourth knuckle (metacarpal) bone in the hand was twice as common in definite cases of Rett syndrome as in other girls of the same age in the right but not the left hand. The X-ray on this page is an example of the short fourth bone in the hand.

• In comparison to other girls, hand bones of girls with Rett syndrome appear to be more 'mature' at an earlier age than we would expect. This was most apparent in the younger group where bones appeared longer than would be expected whilst in the older group bones were much shorter.





BONE THINNING

The degree of bone thinning or 'osteopenia' was also assessed when reviewing the X-rays because girls with Rett syndrome seemed to suffer from fractures more often than we would expect.

• Girls with Rett syndrome were more likely to fracture or break a bone than we would expect. By 1999, about one third (35%) of girls in the study had suffered from a fracture.

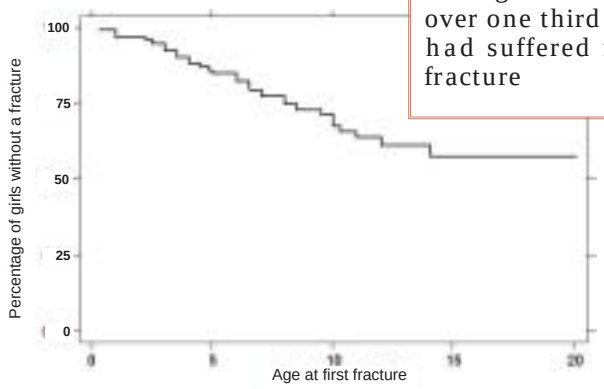
• This result is especially interesting considering that girls with Rett syndrome are less likely to be taking part in vigorous sporting activities or games which can lead to accidents.

Other studies including a recent Italian study using bone densitometry and ultrasound are now also making similar observations. In 2002 and beyond we plan to further investigate this problem in Rett syndrome.

• Over 80% of girls with Rett syndrome had osteopenia which is visible bone thinning on X-ray and in a quarter of girls this was severe.

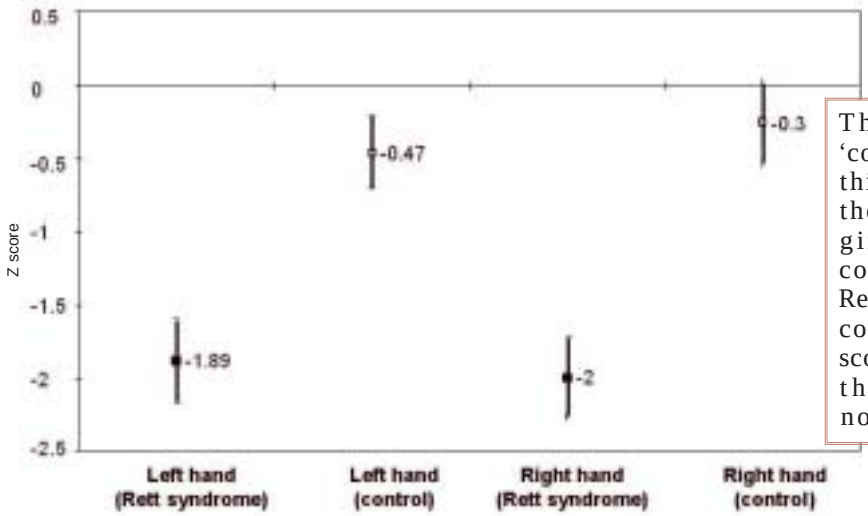
• Some of this bone thinning could be attributed to the use of certain seizure medications.

• Calcium intake was within the normal limits for girls of that age.



This shows that by the age of 15 years, over one third of girls had suffered from a fracture

Cortical thickness: Rett syndrome compared with controls



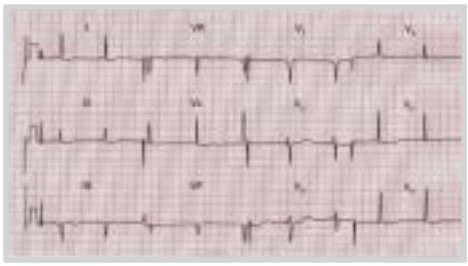
This graph shows that the 'cortical thickness', that is the thickness of the outside part of the bone is significantly less in girls with Rett syndrome compared with girls without Rett syndrome. A score of 0 is considered to be normal and scores less than zero mean that the bone is thinner than normal.

Clinical Studies

At the Children's Hospital at Westmead, New South Wales, clinical studies were carried out on a group of 35 girls and women with Rett syndrome between 1996 and 1999.

ECG STUDY

An electrocardiogram (ECG) is a graphical representation of how the electrical impulses travel through the heart. It is an extremely useful tool for identifying heart abnormalities, such as an abnormal heart rhythm which may be of risk to the patient.



• In this group it was found that part of the heart conduction cycle (termed QT interval) was longer than expected in approximately 25% of girls and young women.

• This abnormality was not associated with any particular age group or type of Rett syndrome, in other words, it was equally common across all ages and severity ranges.

This finding has important implications for the management in Rett syndrome. In particular, certain medications should be avoided in the presence of a prolonged QT interval. In addition, the role of prolonged QT syndrome and its link to problems in the part of the brain called the autonomic nervous system may also be relevant.

L-CARNITINE

Carnitine is a vitamin like substance that is partly made by the body as well as being present in some foods such as red meat and dairy products. The role of carnitine is to transport fatty acids into the mitochondria of the cell to generate energy, especially in the heart, liver and skeletal muscle. The mitochondria of the cells are the parts that generate energy (the 'cell powerhouses').

A case history was published in 1994 about a woman with Rett syndrome who was treated with L-carnitine. There appeared to be improvement in functioning, particularly in the areas of social skills and communication.

As a result of this single case report, a clinical trial of L-carnitine was conducted at The Children's Hospital at Westmead, New South Wales, to evaluate its effectiveness in improving communication and functioning. The style of the study was a randomised double blind crossover control trial, whereby some girls were given L-carnitine and others a 'placebo' and then after a break the treatments were reversed. Neither the families nor the doctors were aware when each girl was taking the L-carnitine or when they were taking the placebo.

• The findings of this initial trial warranted continued study as the L-carnitine was found to be effective in some girls in improving their level of alertness, energy and sleep pattern.

• A long-term follow-up study was then conducted with L-carnitine being administered to 20 of the original 35 girls and women with Rett Syndrome.

• One of the main significant findings was an improvement in sleep efficiency.

2000 Study: Follow-up questionnaire

The aim of the follow-up questionnaire was to collect important information concerning the long-term prospects for the child with Rett syndrome in relation to functional ability, medical and behavioural issues. Information was also specifically collected about use of medical, therapy and other services, schooling and post-school options.

• 152 families completed the follow-up questionnaire in mid-late 2000. The age of children and young people on whom this questionnaire was completed ranged from 2 to 24 years.

Information was collected using a comprehensive questionnaire which was developed in collaboration with several clinicians and researchers, both here and overseas.

The questionnaire comprised 15 sections.

Follow-up Questionnaire

- Feeding & meal times
- Health problems
- Measurement
- Family issues
- Functioning
- Equipment
- Therapies
- Hand use & handedness
- Schooling, post-school care
- Medical & health care
- Medical conditions
- Behaviour
- Puberty

An important element of the questionnaire was a version of the WeeFIM (the Functional Independence Measure for Children). The WeeFIM measures typical performance of children in essential self-care, mobility, communication-social learning tasks. We know that the objective measurement of functioning and ability can be difficult in Rett syndrome because of the limitations with verbal communication. Nevertheless, quantification of functioning is important so that needs can be identified and appropriate support provided to families and carers.

Following the success of our Internet study in 1999, we gave parents the option of completing the document using the Internet. This has proved to be time efficient for both families and our research team and avoids any error that can be associated with manually entered data.

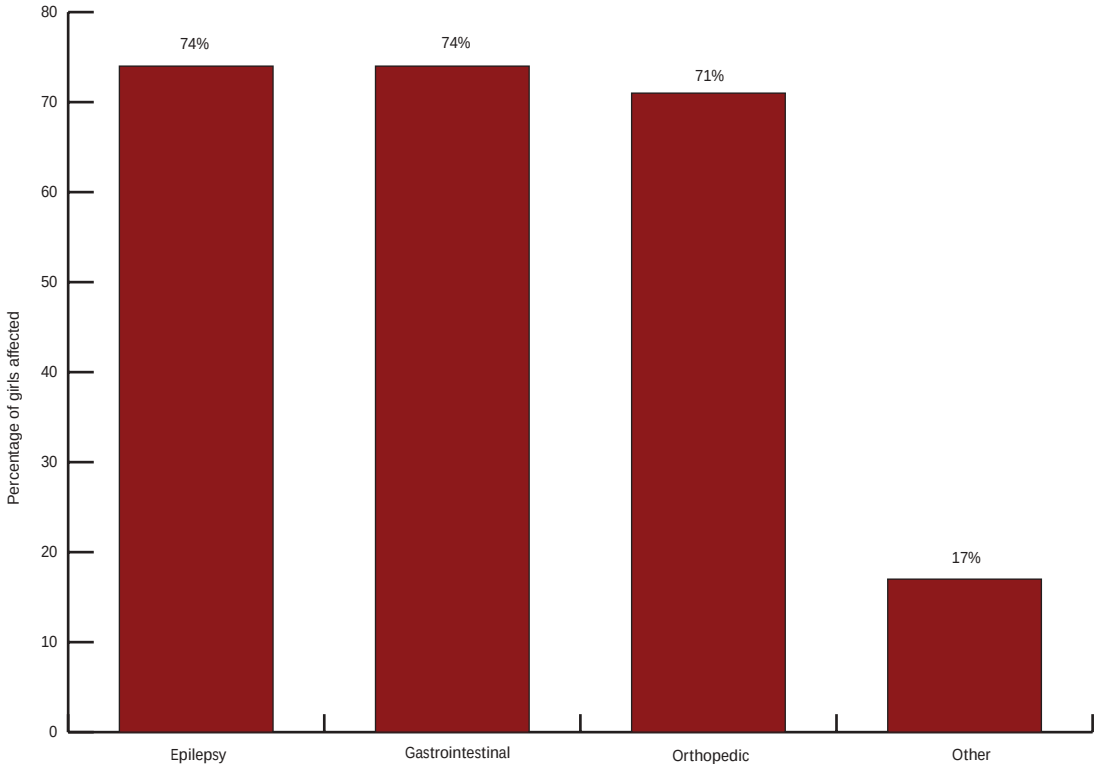
The following information is based on parents' responses to the 2000 questionnaire.

MEDICAL CONDITIONS

Whilst many girls with Rett syndrome are very healthy, Rett syndrome can be associated with a number of medical problems. Most girls with Rett syndrome have at least one health problem requiring ongoing management.

The graph below shows the proportion of girls experiencing the various medical problems typically associated with Rett syndrome.

Medical conditions in girls and women with Rett syndrome



Type of condition

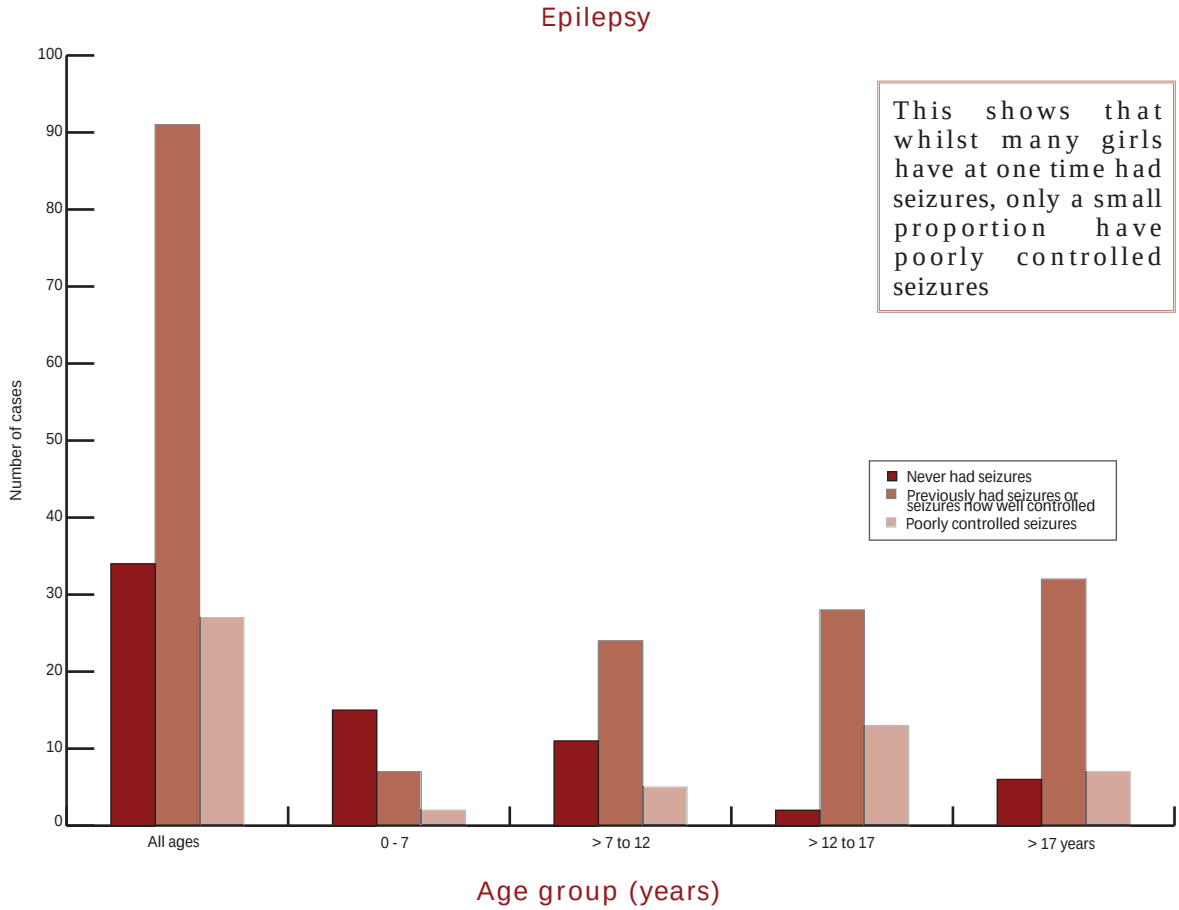
• The most common problems in Rett syndrome are those that affect the brain, gastrointestinal and musculoskeletal systems.

• Almost all girls with Rett syndrome have one of these problems and just half of the Australian girls and young women have problems in all three areas.

EPILEPSY

Epilepsy is a very common disorder in girls with Rett syndrome. The diagnosis of epilepsy is usually made by an EEG (electroencephalograph) test after parents have noticed their child having seizures.

- Over three quarters of Australian Rett syndrome girls suffer from this condition.
- Almost all of the girls with epilepsy are on medication to control their seizures.
- Two thirds are on more than one medication to manage this condition.



During 2000, 164 families took part in the calendar study. Parents recorded the number of seizures occurring in their daughter.

- Almost two-thirds had at least one seizure during that year.
- When averaged over all girls and every seizure experience (including multiple seizures), each girl had approximately one seizure per week.

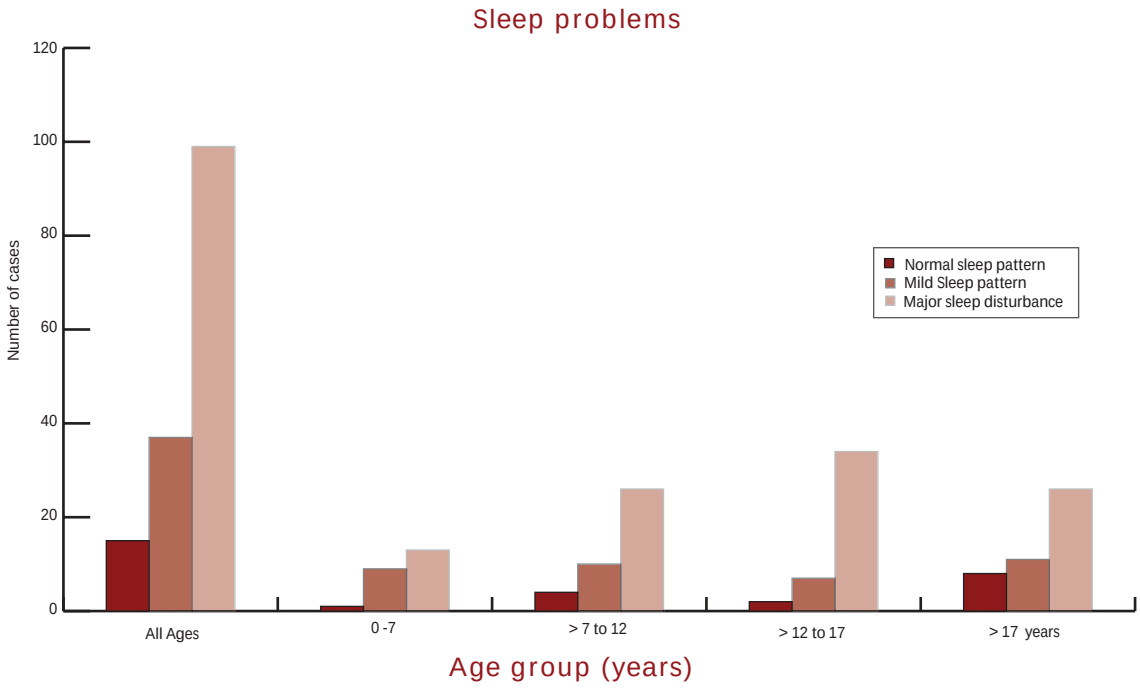
SLEEPING

Sleep disorders are one of the earliest problems in Rett syndrome and can have an enormous impact on the family. Furthermore, sleep disorders can be difficult to treat. Sleep disorders include night laughing, awakening during the night, teeth grinding, screaming and terrors. Children with sleep disorders can undergo a sleep 'study' at a children's hospital to assess their sleeping patterns.

- Almost all (90%) of girls have had problems with sleeping.
- The most common sleeping problem was night laughing affecting about three-quarters of the Australian girls.
- The adjacent table shows a variety of sleep problems ever experienced by Australian girls and women with Rett syndrome

Sleep problem	Percentage
Night laughing	73
Teeth grinding	59
Screaming	53
Seizures at night	42
Sleep talking	13
Sleep walking	3

This graph shows that the majority of girls have had a major sleep disturbance. However a small proportion of girls have always had a normal sleep pattern.



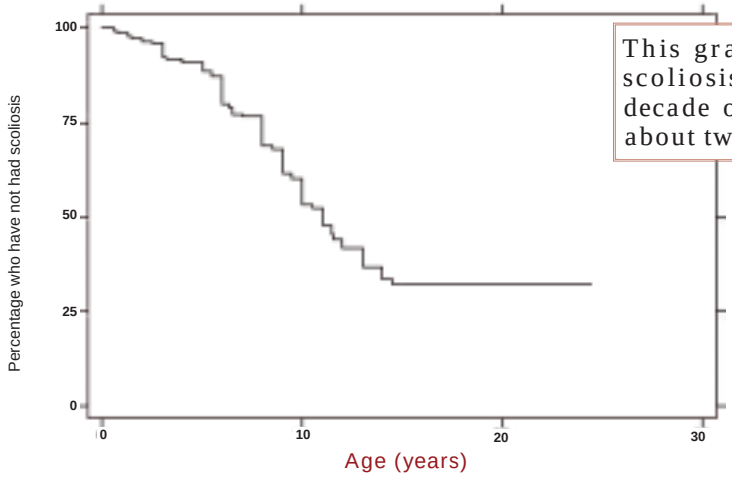
2000 study

SCOLIOSIS

Many girls are affected by scoliosis and many parents notice the condition at an early age. Treatment for scoliosis can be difficult and often includes bracing and sometimes surgery.

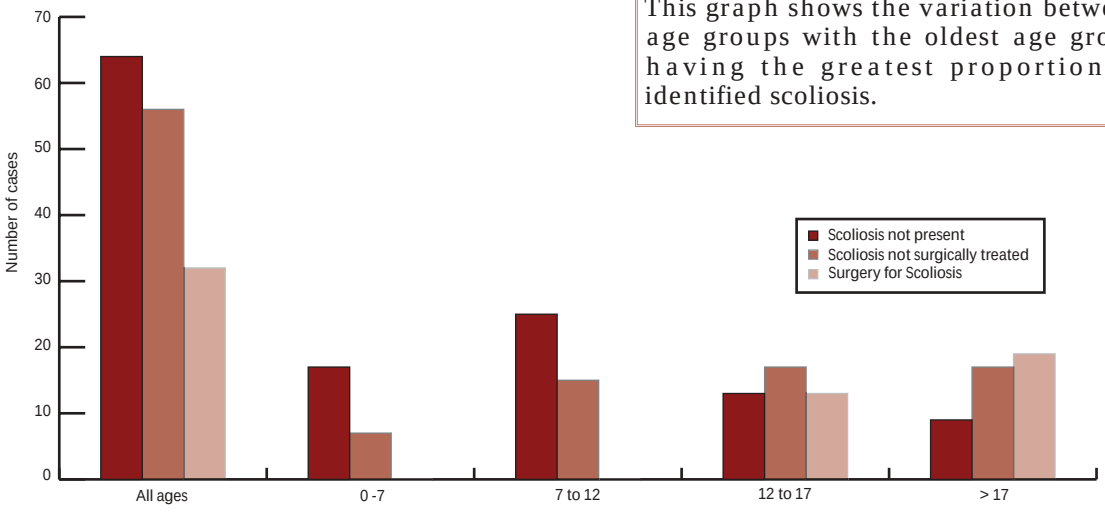
- Over half of girls had been diagnosed with scoliosis.
- Just under half of those girls had undergone surgery for scoliosis.

Scoliosis in girls and women with Rett syndrome



This graph shows that the onset of scoliosis is mainly during the first decade of life. By the age of 14 years, about two-thirds of girls had scoliosis.

Scoliosis in Rett syndrome



This graph shows the variation between age groups with the oldest age group having the greatest proportion of identified scoliosis.

The presence of scoliosis can have a major impact on breathing, posture, overall functioning and quality of life. As this condition is so common in Rett syndrome, we plan to study the effectiveness of bracing, surgery and therapies over time.

GASTROINTESTINAL

Many parents also report that their daughters have difficulties with the digestion of food. Problems with digestion can occur at any place in the gastrointestinal tract for example at the level of the esophagus or gullet (eg reflux) or in the large bowel (eg constipation).

• The majority (74%) of families reported that their daughter had a gastrointestinal problem.

• Most commonly this was constipation affecting almost two thirds of girls.

• Gastro-esophageal reflux was experienced by almost one quarter of girls.

• Rare gastrointestinal problems mentioned by families included diarrhoea, ulcerated bowel, and cholecystitis.

• A large proportion of families have made dietary changes to help with the bowel problem.

• Several girls have had surgery to correct their bowel problem.

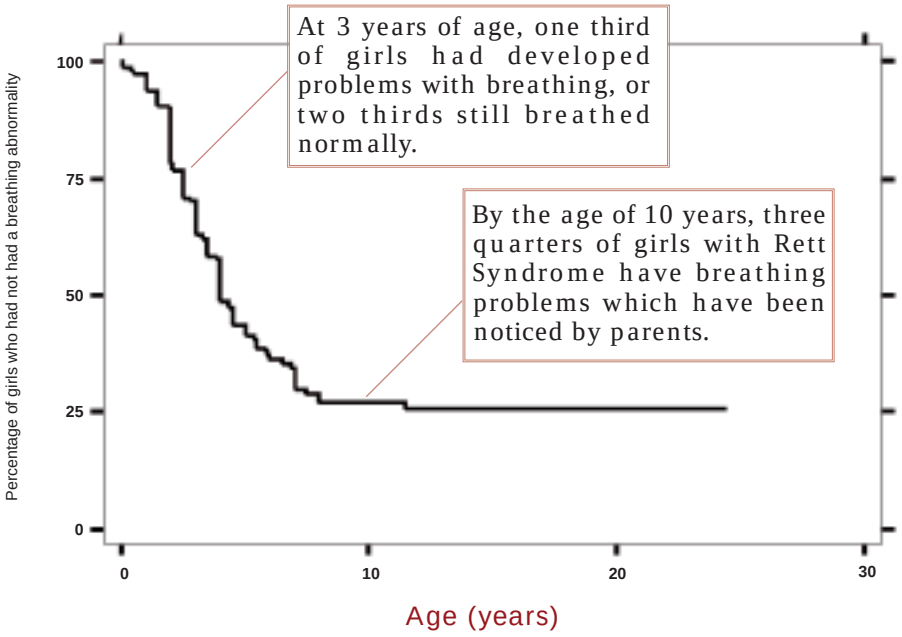
BREATHING PROBLEMS

Breathing problems can include hyperventilating, episodes of breath-holding and air swallowing. Breathing abnormalities may be particularly associated with particular events or emotions such as excitement.

- 74% of Australian families stated that their daughter had breathing abnormalities.
- No girls or women had been effectively treated for breathing problems.

This graph below demonstrates the age at which breathing abnormalities appeared.

Breathing problems in girls and women with Rett syndrome



Breathing problems are related to part of the nervous system called the autonomic nervous system which controls functions such as sleep, breathing, heart rate and digestion. Studies by researchers in Scotland have demonstrated that the majority of girls with Rett syndrome have abnormalities in this system, even though breathing problems may not have been identified by parents.

FEEDING

We know that feeding and meal times can sometimes be difficult for girls with Rett syndrome. There is a huge variation in the extent to which girls can feed themselves.

• Just under half of girls have no difficulty eating most foods.

• However almost three quarters of families still needed to specially prepare meals for their daughter (eg by finely chopping or mashing).

• About one tenth (12.5%) of girls and young women in the study had either a gastrostomy button or a nasogastric tube.

• 40% had special routines or utensils at meal times.

Many families comment that their daughters have large appetites but nevertheless are not able to gain weight as well as their siblings and peers.

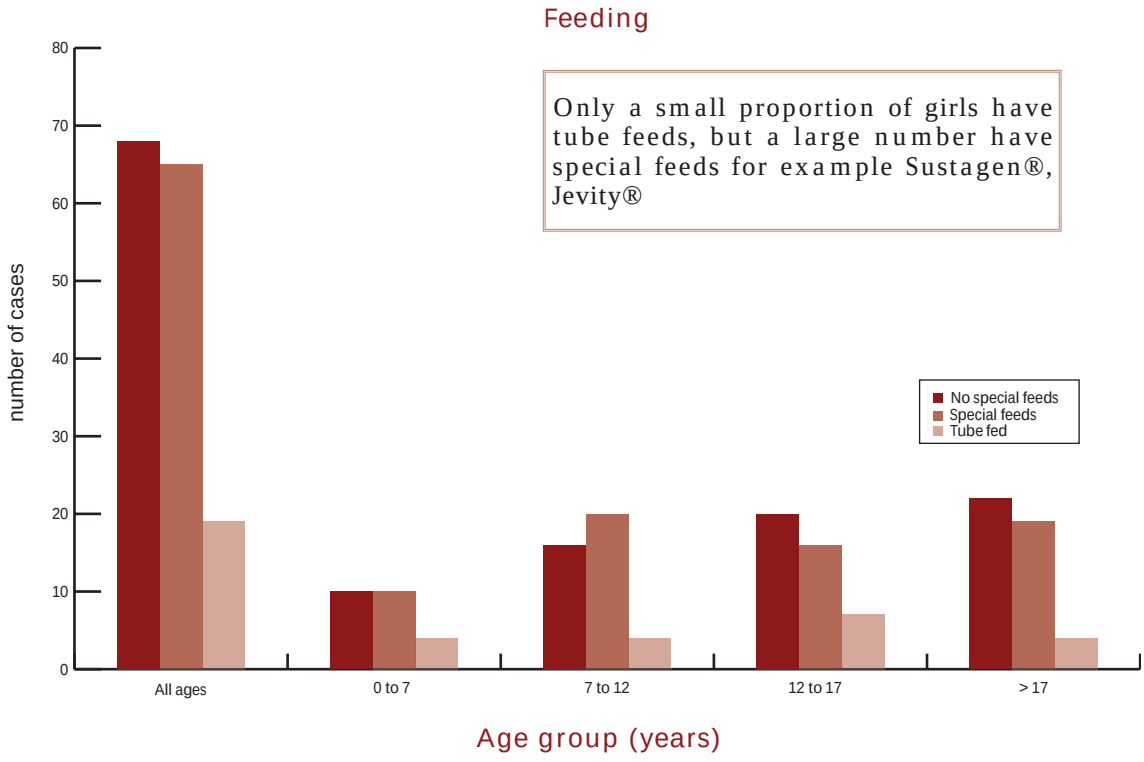
• Just over one quarter seem to eat more than you would expect, however about half ate what you would expect.

• The average body mass index (BMI) of girls in the study was 17.5 indicating that most girls and women were lighter than would be expected for their height.

Age group	Body mass index*
All ages	17.5
0-7 years	15.4
7-12 years	15.5
12-17 years	16.6
17 years	21.0

***Health weight range = 20-25**

Body mass index is a number calculated from an individual's height and weight. It is used as a rough guide for nutritional status.



The insertion of gastrostomy buttons has become a common practice in Australia. It will be important to evaluate the impact of this on the health and nutrition of girls with Rett syndrome as well as the impact on the family of tube feeding, be it negative or positive.

HEALTH CARE USE

We were interested in the patterns of health care use in Rett syndrome. Many girls with Rett syndrome have extremely good health and are no more likely than their peers to require medical attention. Others have multiple medical problems and require ongoing medical treatment and hospital admissions.

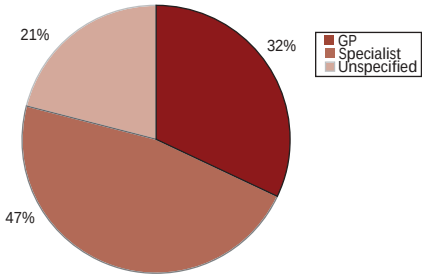
Medical appointments

Our results show that:

- Almost all (97%) of girls or women attended a medical appointment in 1999.
- The average number of medical appointments for each girl or women was 9.

The graph alongside shows the type of doctors appointments.

Medical appointments in girls and women with Rett syndrome



Hospital stays

Our results show that:

- About one third (35%) of girls and young women in the study had a hospital admission in the year studied. The table adjacent shows the reasons for hospital admission.
- Of those who had a hospital admission during 1999, about half had one hospital admission. Only 5 girls or women had 5 or more admissions.

Main reason for admission to hospital

Reason	Percentage of hospital admissions
Gastrointestinal	18
Neurological	18
Dental	9
Ear, nose, throat	8
Test or procedure	8
Orthopedic	8

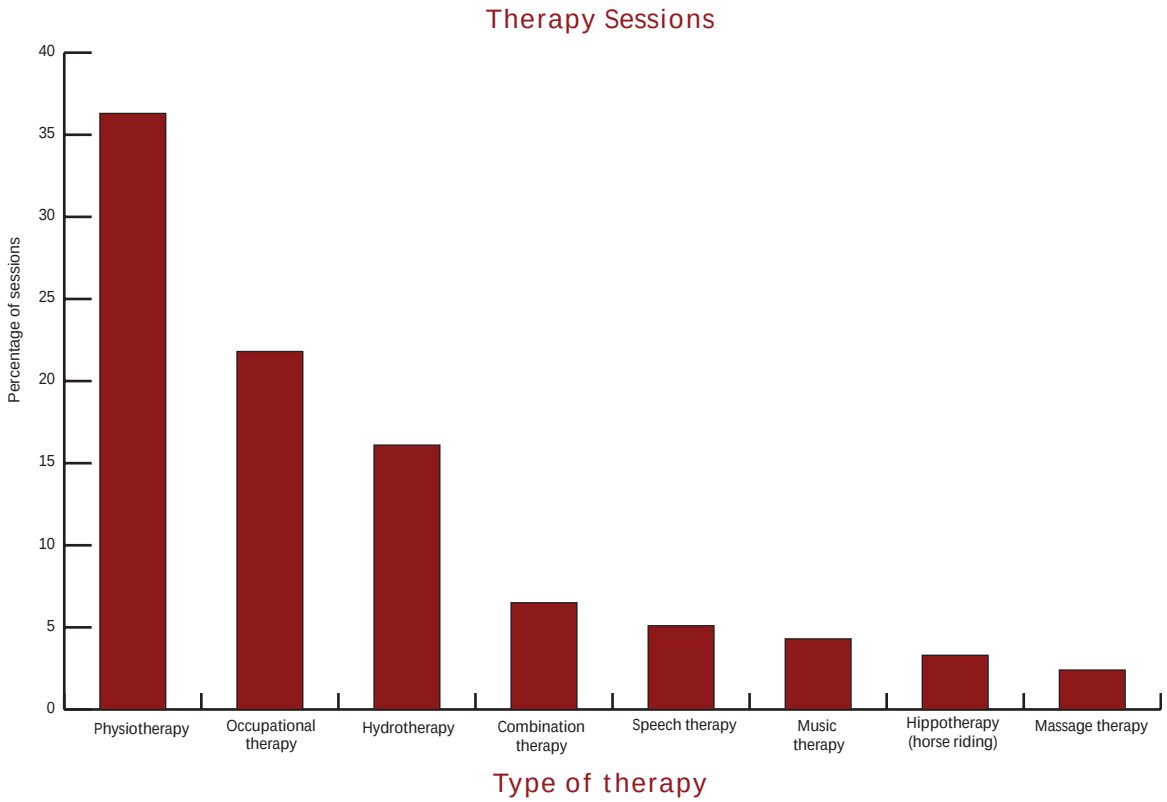
- The longest hospital stays were associated with orthopedic procedures (eg spinal fusions, hip operations).

THERAPY USE

• About two thirds (68%) of girls and young women in the study received therapy in the year studied.

• The majority of therapy sessions were conducted in a regular class setting.

The graph below shows the proportions of types of therapies received.

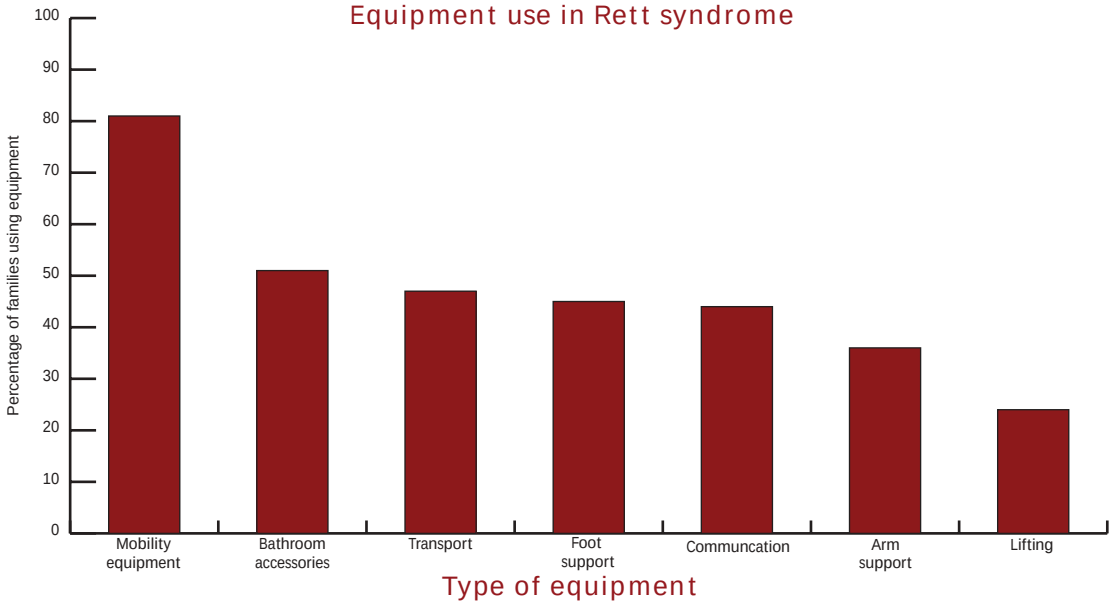


• Less commonly mentioned therapeutic activities included bike riding, sessions with a chiropractor and dancing.

Despite the fact that a large proportion of girls and women receive therapy services, there has been little attempt to evaluate its effectiveness. In addition, many families report difficulty in accessing therapy for their daughters. Over the coming years, we plan to study the patterns of therapy use in Rett syndrome and determine its impact on the functioning and health of girls and women.

EQUIPMENT

Many families use equipment to assist with their daughter's functioning. The graph below shows the proportion of families that use different types of equipment with their daughter.



Parents gave examples of the types of equipment that they used with their daughters.

- Mobility equipment included wheelchairs, standing frames and walkers.
- Bathroom accessories included shower/bath chairs, commodes and hand rails.
- Aids with transport included booster seats and specially installed hoists. A number of families had purchased vans in order to transport their daughters.
- Foot supports included foot cups, AFOs (arthotic foot orthoses) and orthotics.
- Communication aids included the Big Mac Switch, 'cheap talk' and communication board.
- Arm supports included hand, arm and elbow splints.
- Lifting aids included fixed and transportable hoists for transferring their daughter.

Just under half of families had alterations made to the house. Most commonly families had made modifications to the bathroom or installed ramps to aid with wheelchair movement.

About a quarter of families felt that they had difficulty obtaining the equipment and less than half felt that they had adequate financial support with equipment. Many families made the comment that there was an unacceptable delay in government assistance for this equipment so they opted to meet the costs themselves.

It is clear that the majority of families have needed to attain equipment to assist with their daughter's functioning. Furthermore, many families have commented on the financial expense and challenges associated with acquiring this equipment. We are planning to carry out an economic evaluation to determine the cost of this to both families and the community.

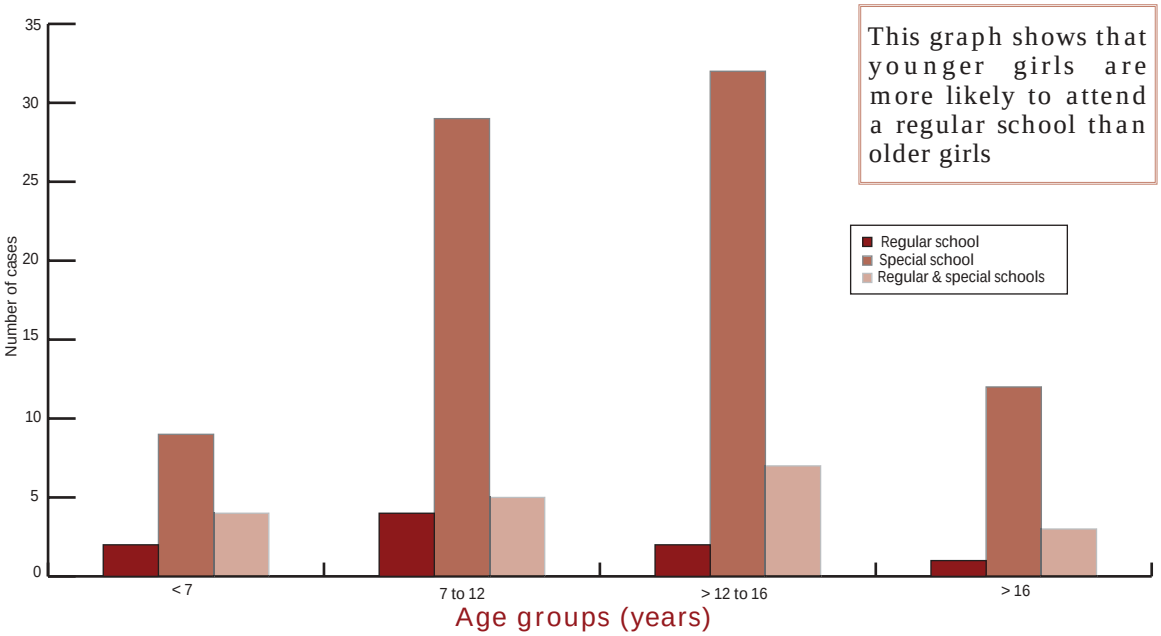
EDUCATION

Throughout Australia there was some variation in the educational settings for girls with Rett syndrome.

In Australia, three quarters of the girls in this study were of school age.

- Just over two-thirds of those girls attended a special school only
- Nine girls attended both a special school and a regular school
- Almost one fifth of girls were taught at a main-stream school – most of these girls attended a special education unit at the school.
- Several girls were home-schooled.

Schooling types for girls with Rett syndrome



Three quarters of parents with school-aged children felt that the educational needs of the child were being met by the current arrangement. Ten percent felt that the needs of their daughters were not being met. The main criticism was that their child was not getting the necessary one-on-one attention. Many parents made comments about the inadequacy of resources.

These results are important for the long-term planning of educational services for children with Rett syndrome and similar disabilities. Of interest is the considerable number of children who are attending main-stream schools. With the move towards inclusive schooling, it is important that teachers are adequately supported and trained.

FUNCTIONING

Whilst there is variation in the abilities of girls with Rett syndrome it is considered to be a severely disabling disorder. One of the difficulties in measuring abilities in Rett syndrome is that most girls have problems communicating.

In order to measure functioning, we used the WeeFIM (Functional Independence Measure for Children). This has been used on thousands of children around the world with a variety of disabilities. The WeeFIM produces a maximum score of 126 for independent functioning in an eight year old child without a disability.

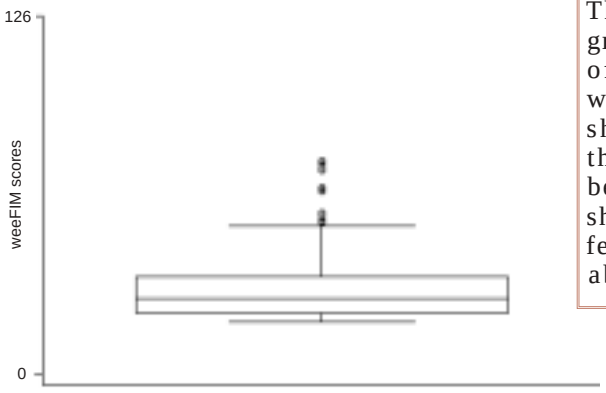
• The average score for girls with Rett syndrome in Australia was 29.

• There was no significant difference in the score between girls who did have a mutation and those who did not.

• However there was a large range in the WeeFIM score (18-75).

Age group	Average score	Lowest score	Highest score
< 7 years	29	18	52
7-12 years	32	18	74
12-17 years	27	18	57
> 17 years	28	18	75
All ages	29	18	75

WeeFIM scores in Australian girls and women with Rett syndrome



The large box in this graph represents 50% of the girls and women studied. It shows that most the the girls have a score between 20 and 40. It shows that there are a few girls with scores above 50.

Areas of strength

Girls with Rett syndrome performed most strongly in the area of mobility where 39% of girls and women were mobile, 12% were able to manage stairs independently or with assistance, 22% were able to get in and out of a chair alone or with assistance, and 11% were able to transfer in and out of a bath or shower, either independently or with assistance.

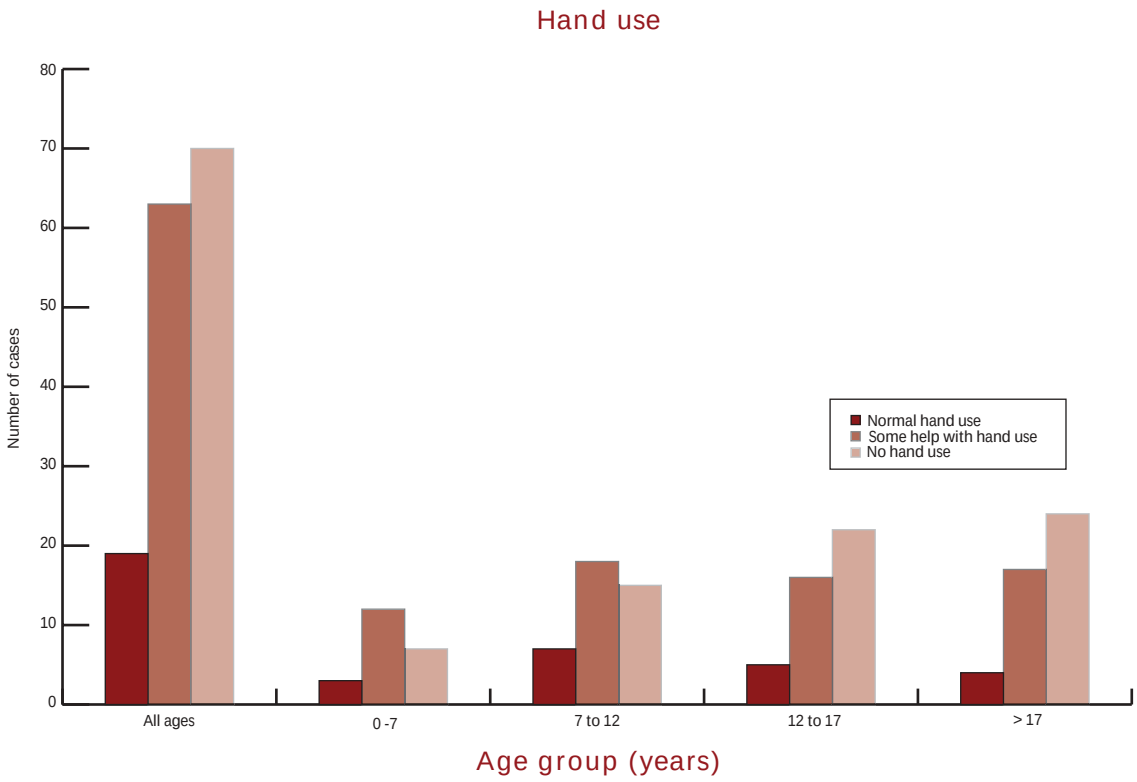
Areas of weakness

Girls had most difficulty with communication skills.

HAND FUNCTION

Loss of hand use is a characteristic feature of Rett syndrome. Many girls lose fine motor skills and are no longer able to use their hands functionally, for example to feed themselves or manipulate toys.

The graph below shows the hand use in different age groups. Whilst the majority of girls have no functional hand use, a small number were considered to have normal hand use.



FAMILY

We know that having a child with a disability can have a significant impact on the family unit. Families were asked about the impact of Rett syndrome upon the other children in the family.

• Over half of families felt that there were advantages for their other children in having a sister with Rett syndrome.

• The most common advantage mentioned was that the other children in the family are more accepting of other children and people with disabilities and differences in general.

• Over three quarters (85%) felt that there were also disadvantages.

• The most common disadvantage mentioned was less time available for the other children.

PUBERTY

Sexual development and the onset of menstrual periods is often a concern reported by parents.

In the follow-up study:

• 21% of families felt that their daughter's sexual development was different to what they would expect for her age.

• Differences varied and included both the early development of pubic hair and a relatively late menarche (first period).

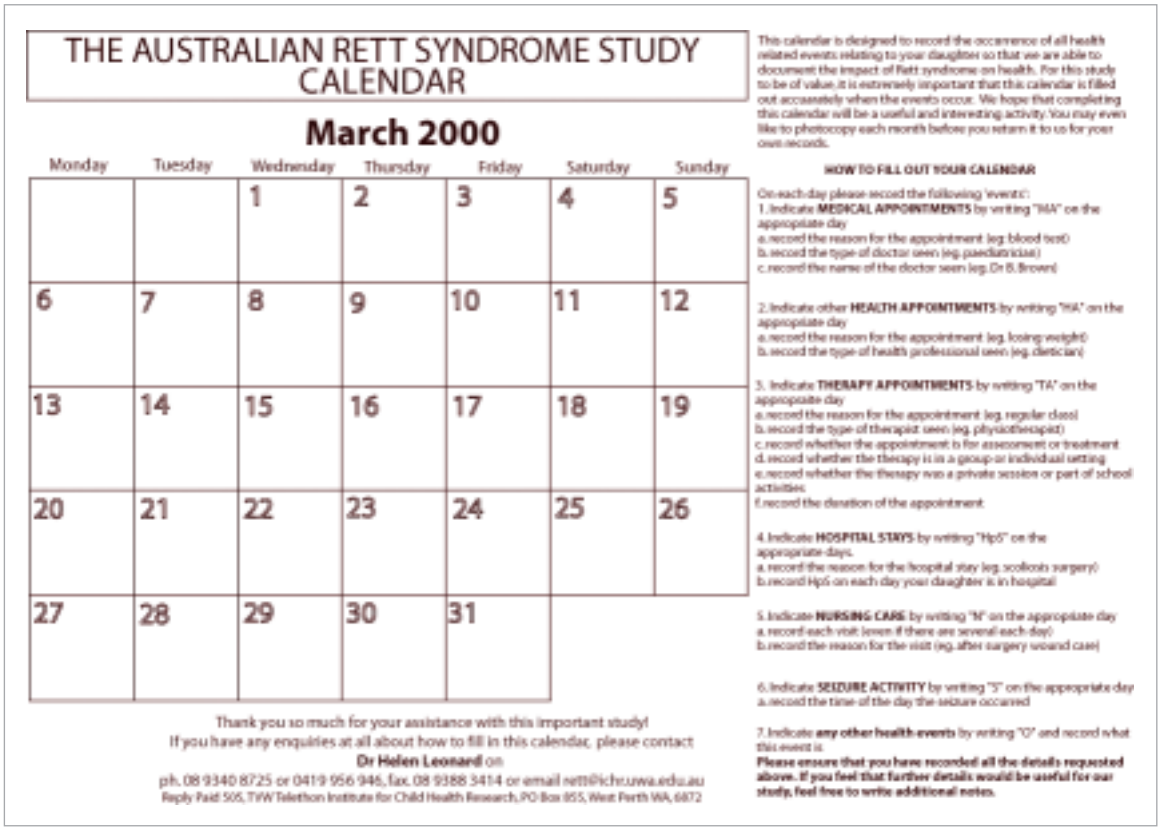
• In almost half of those girls and young women who menstruated families or carers reported that they had problems with managing menstruation.

• About one quarter of this group were on medication to control the periods.

• Very few had undergone surgical procedures to manage menstruation.

CALENDAR STUDY

During the year 2000, 160 families were involved in the calendar study as part of the 2000 Follow-up study. The aim of the study was to collect information about day-to-day aspects of the health of girls and young women with Rett syndrome. Information on medical, therapy and health appointments, as well as the frequency of seizure activity and medications was recorded on a daily basis for a period of 12 months.



THE AUSTRALIAN RETT SYNDROME STUDY CALENDAR

March 2000

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

Thank you so much for your assistance with this important study!
If you have any enquiries at all about how to fill in this calendar, please contact:
Dr Helen Leonard on
ph. 08 9340 8725 or 0419 956 946, fax. 08 9388 3414 or email nett@ichr.uwa.edu.au
Reply Paid 505, TVW Telethon Institute for Child Health Research, PO Box 855, West Perth WA, 6872

This calendar is designed to record the occurrence of all health related events relating to your daughter so that we are able to document the impact of Rett syndrome on health. For this study to be of value, it is extremely important that this calendar is filled out accurately when the events occur. We hope that completing this calendar will be a useful and interesting activity. You may even like to photocopy each month before you return it to us for your own records.

HOW TO FILL OUT YOUR CALENDAR

On each day please record the following 'events':
1. Indicate **MEDICAL APPOINTMENTS** by writing "MA" on the appropriate day
a. record the reason for the appointment (eg. blood test)
b. record the type of doctor seen (eg. paediatrician)
c. record the name of the doctor seen (eg. Dr B. Brown)

2. Indicate other **HEALTH APPOINTMENTS** by writing "HA" on the appropriate day
a. record the reason for the appointment (eg. losing weight)
b. record the type of health professional seen (eg. dietician)

3. Indicate **THERAPY APPOINTMENTS** by writing "TA" on the appropriate day
a. record the reason for the appointment (eg. regular class)
b. record the type of therapist seen (eg. physiotherapist)
c. record whether the appointment is for assessment or treatment
d. record whether the therapy is in a group or individual setting
e. record whether the therapy was a private session or part of school activities
f. record the duration of the appointment

4. Indicate **HOSPITAL STAYS** by writing "Hp5" on the appropriate days.
a. record the reason for the hospital stay (eg. scoliosis surgery)
b. record Hp5 on each day your daughter is in hospital

5. Indicate **NURSING CARE** by writing "N" on the appropriate day
a. record each visit (even if there are several each day)
b. record the reason for the visit (eg. after surgery wound care)

6. Indicate **SEIZURE ACTIVITY** by writing "S" on the appropriate day
a. record the time of the day the seizure occurred

7. Indicate **any other health events** by writing "O" and record what this event is.
Please ensure that you have recorded all the details requested above. If you feel that further details would be useful for our study, feel free to write additional notes.

In order to compare this information with a group of girls without Rett syndrome, a group of 52 Year 6 students from St Mary's Anglican School (Perth, Western Australia) took part in the calendar study. A similar process was undertaken with students recording their illnesses, medical, therapy and health appointments as well as medications over a six-month period.

This was a mutually beneficial experience, with the schoolgirls gaining an increasing understanding and appreciation of Rett syndrome, intellectual disability and the research process.

Further collection of this information will allow us to compare the daily life of girls with Rett syndrome with girls who do not have this disability.

In 2002, these include high school students from Lockridge Senior High School and Helena College as well as university students from Murdoch University. Students have used the Internet to enter their own health information.

Other studies about Rett syndrome

INTERNATIONAL RESEARCH

Our study has been an active participant in international research on Rett syndrome since its inception.

Our collaborators include:

- Dr Angus Clarke: Cardiff University

  Mutation screening (1994 onwards)

- Professor Michael Msall: Brown University

  Measurement of functioning in Rett syndrome and Down syndrome (1997 onwards)

- Dr Richard Umansky: UCLA

  Handedness (1999 onwards)

- Dr Carolyn Schanen: UCLA

  Rett syndrome in boys

- Ms Rebecca Mount: Institute for Child Health, London

  Behavioural features

- Dr Yushiro Yamashita: Japan

  Atypical Rett syndrome: R133C mutation

- Dr Alison Kerr: Glasgow University

  Guidelines for the classification of Rett syndrome

INTERNET STUDY

The "Rettnet" is an internet email list set up by the International Rett Syndrome Association. Subscribers to the list include parents, therapists, teachers, doctors and other persons interested in the syndrome. Subscribers post messages to the list containing questions or comments about any aspect of the syndrome and as a result a discussion can be generated about an issue. Topics discussed range from medical problems such as epilepsy to education and therapy use.

During the year 2001 we carried out a study involving subscribers to the Rettnet. This study aimed to assess the value of the Rettnet and compared the information derived from it to information from medical professionals.

Key findings from this study:

• Most subscribers joined the Rettnet in order to gain information about the syndrome.

• Other reasons for joining included the sharing of experiences, to make friends with other parents/carers, for emotional support from other parents/carers.

• Of note was the fact that 41% of subscribers did not know another Rett syndrome family prior to joining the Rettnet.

• Almost all (87%) found that the Rettnet provided helpful advice.

• Almost all (90%) believed that the information was accurate.

CURRENT STUDIES

International Rett Syndrome Phenotype Database.

In association with the International Rett Syndrome Association, we are in the process of developing an international Rett Syndrome Phenotype database which will be linked with the IRSA MECP2 mutation database (based in Sydney).

• The database will be used to collect information from both clinicians and families about the clinical features of Rett syndrome and its effects at different ages.

• This will provide a unique opportunity to collect information more efficiently and on a worldwide scale using the Internet.

• Collecting this information on a large and diverse group of individuals will enable us to accurately provide information about the range of variation in Rett syndrome and attempt to link the mutation type to the clinical symptoms found.

Follow-up study 2002

To understand the development of Rett syndrome and its impact on families over time we will ask families to complete a questionnaire once every two years. The questionnaire for 2002 will be mailed to families in September.

Funding

funding

The Australian Rett Syndrome Study is based at the Telethon Institute for Child Health Research an independent, non-government institution which provides a base for research studies.

Funding for this study and support for attendance at conferences has been provided by:

- The Rett Syndrome Australian Research Fund (previously RSANSW)
- Financial Markets Foundation for Children
- International Rett Syndrome Association
- APEX Foundation for Research into Intellectual Disability
- The Rett Syndrome Association of Australia
- The Friends of the Telethon Institute for Child Health Research
- National Health and Medical Research Foundation (Public Health Research and Development Council)

Presentations

Presentations have been made to a number of local, interstate and international bodies over the past ten years.

2002

"Rett syndrome: evolution from genotype to phenotype"

Human Genetics Society of Australia Conference, Cairns.

"Now that the gene has been found: Describing the phenotype in Rett syndrome using a national database".

Rett Syndrome Research Foundation Conference, Baltimore, USA

2001

Invited as a member of a clinical consensus panel, to review clinical criteria for Rett syndrome and to consider clinical severity scales for Rett syndrome Baden Baden, Germany.

"Rett syndrome in Australia from the nineties to the new millenium".

Human Genetics Society of Australia Conference, Cairns.

"Rett syndrome in Australia from the nineties to the new millenium".

Grand Round, Women and Children's Hospital, Adelaide.

"Rett Syndrome in the new millenium".

Conference of the National Association of Neurophysiology Technicians. Perth.

"Rett Syndrome".

2001 Annual Scientific Meeting of the Australian Association of Neurologists, Movement Disorder Workshop, Adelaide.

2000

"Measuring the burden of disability: preliminary findings using two different approaches."

Middens Mirrors and Mosaics 5th National Conference for Supplementary Children's Service Workers, Fremantle.

"Childhood disability: changing patterns; impact on the child and family and collaborative opportunities for research."

24th Australian Conference in Special Education, Perth.

1999

"Rett syndrome: APSU and beyond".

Annual Scientific Meeting of the Royal Australian College of Physicians, Perth.

1998

"Systems for the management of intellectual disability in Western Australia".

Ostersund, Sweden.

"Bone quality and its effects in Rett syndrome".

Folke Bernadotte International Memorial Conference, Stockholm, Sweden.

"Perinatal and infant deaths in families of girls with Rett syndrome".

Australian and New Zealand Perinatal Society Conference, Alice Springs.

"Rett Syndrome".

Forum on Behavioural Stereotypes in Intellectual Disability. Monash Medical Centre, Melbourne.

"Rett Syndrome".

The National Association of Neurophysiology Technicians. Perth.

"An investigation of familial co-aggregation of other conditions with Rett syndrome".

Conference on Human Genetics:Diversity and Disease. Fremantle.

"The Hands and Feet in Rett syndrome"

Conference on Human Genetics:Diversity and Disease. Fremantle.

"Radiological clues to the neuroendocrine basis of Rett syndrome".

Conference on Human Genetics:Diversity and Disease. Fremantle.

"Lightning strikes twice - a family with Rett syndrome in two generations".

Conference on Human Genetics:Diversity and Disease. Fremantle.

"A boy with Rett-like features".

Conference on Human Genetics:Diversity and Disease. Fremantle.

"Double-blinded crossover trial in 35 females with Rett syndrome".

Conference on Human Genetics:Diversity and Disease. Fremantle.

"Ascertainment of a rare childhood condition in Australia".

The 28th Annual Conference of the Public Health Association of Australia Inc., Perth.

"Families living with Rett syndrome: their needs and social support networks".

World Congress on Rett Syndrome, Gothenburg, Sweden.

"Rett syndrome in Australia: Epidemiological data - distribution of classical and atypical females".

World Congress on Rett Syndrome, Gothenburg, Sweden.

"A case of variant Rett syndrome with unusual neuropathological Findings".

World Congress on Rett Syndrome, Gothenburg, Sweden.

"Further documentation of familial Rett syndrome".

World Congress on Rett Syndrome, Gothenburg, Sweden.

"Skeletal abnormalities in Rett syndrome: Have we found a dysmorphic marker?"

The 8th Annual Scientific Conference of The Australasian Society for Human Biology, Perth.

"Rett syndrome: care and support of the child and family in Australia".

National conference of the Australian Society for the Study of Intellectual Disability, Perth.

"Solving the puzzle of Rett syndrome".

National conference of the Australian Society for the Study of Intellectual Disability, Perth.

"The First Year of the APSU: The perspective of the investigators of Rett syndrome".

Research and Advances Seminar, Princess Margaret Hospital.

"Rett syndrome in Australia".

National conference of the Australian Society for the Study of Intellectual Disability, Newcastle.

"Rett syndrome: Gene to Gesture" .

Forum on Learning Disability, Royal Society of Medicine, London, UK.

"Rett syndrome in Australia"

Annual scientific meeting of Australian College of Paediatrics and the Paediatric Research Society of Australia, Melbourne.

Publications

Colvin L, Fyfe S, Leonard S, Schiavello T, Ellaway C, de Klerk N, Christodoulou J, Msall M, **Leonard H** Describing the phenotype in Rett syndrome using a population database. Archives of Diseases in Childhood In press

Leonard H, Wen X. The epidemiology of mental retardation : challenges and opportunities in the new millenium. Mental Retardation and Developmental Disabilities Research Reviews In press

Leonard H, Petterson B, Bower C, Sanders R. Prevalence of intellectual disability in Western Australia Paediatric and Perinatal Epidemiology In press

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