AGSA
ASSOCIATION OF GENETIC SUPPORT OF AUSTRALASIA
Funded by NSW Health & ADHC | Reg Charity No.CFN15481 / ABN 83 594 113 193 ACN 168 918 625
C/- Garvan Institute Of Medical Research, Level 6, 384 Victoria St Darlinghurst NSW 2010 Australia
Ph: + 61 2 9295 8359 Fax: + 61 2 9295 8181
website: www.agsa-geneticsupport.org.au
email: info@agsa-geneticsupport.org.au

WILLIAMS SYNDROME AUSTRALIA CONFERENCE 19TH – 21ST SEPTEMBER 2014, Macquarie University

Dear All,

Thank you for making our 3rd National conference so special and it was lovely to see the families together and the children chatting and supporting each other. I think you will all agree the WS conference was very worthwhile not only on a personal social level but also to be able to hear firsthand about the latest research. Approximately 150 people including children attended with the majority of people coming on the Saturday.

- 124 Friday,
- 164 Saturday and
- 131 Sunday.
- 96 Attended the Welcome Drinks *(WSA sponsor a tab for$600)*BBQ
- 73 people attended the Saturday night dinner

Sunday was such a lovely day everyone stayed on for the BBQ but only 37 people had registered for the Sunday BBQ - so it was a catering nightmare. The Macquarie University students rallied together and brought extra sausages, salads, rolls and drinks at Macquarie Shopping Centre. Where would we have been without them? Thanks guys. Crunch catering kindly stayed on to cook. The morning and afternoon teas provided by Brenda Cole were delicious and we thank her for generously charging mate's rates which all went together to help the budget.

Prof Richard Webster talk was very interesting especially to know that a tr 76% of WS people have a tremor and its relation to the cortex and pyramidal brain system.

The highlight for me is always the WS workshop, hearing what they have to say about themselves and what is it like living with WS. Below are their comments:-

WS people workshop with Melanie Porter outlined the following points:-

Biggest Achievements for WS Adults

Came first in dressage competition (Chloe)
Work (Trent)
Talk every Friday 5.30 – 6pm night on radio station 104.7FM (Dianne)
Work for a disability company (Sam)

What are some hard things about having WS?

Being teased
Not having a good health system
Keeping friends
Don't get a good education
Being the only one in my family with WS.

The best things about having Williams syndrome:-

Happy (Jacob)
We are all good/fantastic
We like meeting new people and spreading the word
Like people
Encourage each other
Enthusiasm!!!!

The Best things WS about having friendly

Friendly
Family
Being an Aunty/Uncle

Advice from the WS clan

Don't worry about what anyone says because we are all awesome.
We can show people what we are made of
No-one should judge us – we are perfect in every way.
We have the best syndrome in the whole universe.

Advice from WS

Don't let anyone take advantage of you
Always believe in yourself
No matter what cultural difference we have, we still love each other
Be strong
Be powerful
Be awesome

Hard things about having WS

Not being able to tie shoe laces
No-one realizes that we are intelligent
Doing up buttons

Parents discussion workshops

18+

Leaving home

- Options
- Still at home

Or

- Supported accommodation – very difficult to find.

Group homes

- Are they as good as being home?

Positives

- Enjoy their company

Negatives

- Health issues of WS and parents
- Needing social activities
- Emotional well being

Obsessions

- All have some kind of obsession.
-

Parents of 6 – 12 year olds discussion workshop representing two girls and five boys

Strategies that work

- Bribery – positive encouragement (difficult when siblings involved)
- Humour
- Tone of voice

- Structure

School support:

Severe disability list
IQ test
Use of computer/iPad – obsession of use of iPad better when limitations are clearly explained.
Parent from NZ had a full time aide.

Comprehension

What?
Who?
Where?
Why?

Fine Motor

- Initially shakey
- Use of direct teaching hand & wrist placement
- Sky/grass/ground

-Teaching aide scribe child writing
- Better Start funding

- Posting – laminate pictures
  - Key tab with 10 or so illustrations into box at school when work completed.
  - First & Then chart at school

Other Siblings

Happy heart chair/Naughty chair
All need their own activities
Sleeping
Clonoidine
Melatonin
Monkey clock

Girls 12 – 17 Key points discussed by Mums

Anxiety
Social
Depression
Sleep
Obsession
Health Problems
Food,

Neurological findings in Williams syndrome

By Richard Webster

For a long time, researchers interested in William syndrome (WS) have been interested in the associated cognitive and behavioural features. Less attention has been paid to motor abnormalities and the neurological problems that are seen in people with WS. However, these problems can have a significant impact on the quality of life of people with WS. Potentially, these abnormalities may also provide a clue to abnormalities in the function of brain systems in WS.

I am a paediatric neurologist and I am interested in the causes of neurological problems in children and adults. Neurologists are trained in physical examination and use the neurological examination to identify abnormalities in the way that the brain functions. There are characteristic signs on the physical examination, which suggest that there are problems with the fundamental motor control systems of the brain.

In 2009 I was very pleased to be invited to participate in Melanie Porter's ongoing study of William syndrome. The question that Melanie wanted to address was: what causes neurological abnormalities in people with WS? She was also interested in whether these

neurological problems related to abnormalities in the structure of the brain and how the genetic abnormalities that cause WS are associated with these problems.

Previously, a small number of studies have reported abnormal neurological findings in children and adults with WS. In 1989, Trauner and others compared the neurological and motor development of children with WS with children with Down syndrome. They found that children with WS had slower motor development, lower muscle tone, jumpier reflexes and signs of abnormal cerebellar function (one of the motor control systems). A larger study in 1996 (Catherine Chapman and others), also found that muscle tone was low in younger children but then increased after 8 years of age. They also noted that the majority had abnormal reflexes but did not find abnormalities of cerebellar function. In 2007, a study of 47 adults (Gagliardi and others) confirmed the finding of abnormally brisk reflexes but noted abnormalities of the extra-pyramidal motor control system and again reported abnormalities of cerebellar function. In summary, the studies to date have found abnormalities in motor development but there is conflicting evidence as to which neurological systems are involved. Our current study aims to resolve these discrepancies.

To date we have studied 32 people with WS and 26 people without WS (normal controls). Both groups go through the same examination according to a strict protocol. All subjects have had video recordings made. These are then reviewed by myself and by two other neurologists (experts in the neurology of movement) so that we can accurately categorise the problems that we see.

The results mentioned below are preliminary, but we have found that the majority of children and adults with WS studied have abnormal motor function in particular:

- **Abnormal motor control of speech – 21%**
- **Tremor – 76%**
- **Slowing of rapid alternating hand movements (dysdiadochokinesia) – 88%**
- **Abnormally jumpy reflexes – present in most people with WS**

The practical implication of these abnormalities in motor function is that people with WS are likely to find it more difficult to perform tasks that require highly developed motor skills. *The motor difficulties that people with WS experience are not explained by their intelligence and reflect abnormal function of the neurological systems that are required for movement.* As this research progresses, we hope to better understand which neurological systems are involved and why.

I would like to thank all the people who have participated in this study and Williams Syndrome Australia for sponsoring this research. It has been very interesting and good fun. I will keep you updated with the progress of this research.

PROGRAM OF RESEARCH INTO WILLIAMS SYNDROME: LATEST FINDINGS AND FUTURE DIRECTIONS

by *Dr Melanie Porter*

Melanie and her international team of researchers are studying how gene anomalies in the Williams syndrome (WS) region affect brain functioning. Conferences are not only a great way for families to catch up, but they also provide an opportunity for us to inform families of our latest research findings and to build on this knowledge by collecting more data through research.

Research Findings from the 2007 WS Conference

Before and during the WS conference in 2007 Melanie and her genetics collaborator, Dr May Tassabehji, collected blood samples from over 50 individuals diagnosed with WS for genetic analysis. At the same time, they collected data on mental health and social and cognitive abilities.

Williams Syndrome Conference, Macquarie University, 2007

The main Findings from this work included:

Genetics:

Blood samples were analysed and suggested that the majority of WS individuals displayed a ~1.6Mb (~26 gene) deletion. A high proportion (18%) of the cohort, however, displayed a larger 1.8Mb (28 gene) deletion and some individuals displayed other atypical deletions involving genes within the WS critical region. There were some differences between those with the standard ~1.6Mb deletion and those with the slightly larger 1.8Mb deletion or an atypical deletion in terms of their cognitive, social and mental health functioning (see section 'Putting it all together' below).

Porter, M., Dobson-Stone, C., Kwok, J., Schofield, P., Beckett, W., & Tassabehji, M. (2012). A role for transcription factor GTF2IRD2 in executive function in Williams-Beuren syndrome. *PLoS One*, 7(10), e47457.

Mental Health:

50 parents completed comprehensive interviews to ascertain a life-long psychological history of their son/daughter with WS. The main findings were as follows:

- 42% had never experienced a mental illness
- 26% had taken(or were taking) medication for a mental illness
- 3% had a depressive disorder in childhood, this increased to 25% in adulthood
- 10% had a diagnosis of generalised anxiety disorder, this increased to 25% in adulthood
- Rates of specific phobia were 37% in childhood and decreased to 20% in adulthood
- 20% of the sample had a diagnosis of Attention Deficit Hyperactivity Disorder (higher rates of 33% were reported in children)

We also gathered information on the mental health of parents and found:

- 16% of parents had a current or previous diagnosis of depressive disorder
- <1% of parents had a current or previous diagnosis of an anxiety disorder

Dodd, H.F., & Porter, M.A. (2009). Psychopathology in Williams Syndrome: The Effect of Individual Differences Across the Life Span. *Journal of Mental Health Research in Intellectual Disabilities*, 2, 89-109.

Social:

Social Approach

Preschool children with WS were introduced to two separate strangers in a laboratory-based play paradigm during the WS Conference in 2007. Melanie and her PhD student at the time, Helen Dodd, wanted to know if WS children were just as likely to approach strangers if they wore plain-clothes or a burka (which covered the face and body). This would tell us whether something visual was driving the unusually high social approach in WS.

Melanie and Helen found that WS pre-schoolers were significantly more likely to approach the strangers than typically developing (TD) pre-schoolers overall, and, unlike TD children, for WS children the level of approach did not decrease towards those strangers wearing a burka. This suggests, contrary to accounts in the literature, that the salience of the face and other social visual cues cannot fully account for the unusual social drive observed in WS. Other theories include abnormal brain functioning of the prefrontal cortex and/or amygdala and a positive cognitive bias.

Follow up studies by Melanie and her Masters students indicate that WS individuals do show a positive bias in the way they perceive and interpret other people's facial expressions and intentions. For example, WS individuals are less likely to think someone has a negative intention and they pay more attention to happy than angry or threatening faces when compared to typically developing individuals.

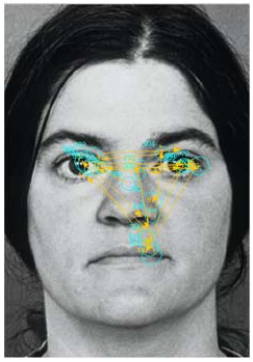
Dodd, H.F., Porter, M.A., Peters, G.L., & Rapee, R.M. (2010). Social approach in preschool children with Williams syndrome: The role of the face. *Journal of Intellectual Disability Research*, 54(3), 194-203.

Dodd, H.F., & Porter, M.A. (2010). I see happy people: attention towards happy but not angry facial expressions in Williams syndrome. *Cognitive Neuropsychiatry*, 15(6), 549-567 doi:10.1080/13546801003737157

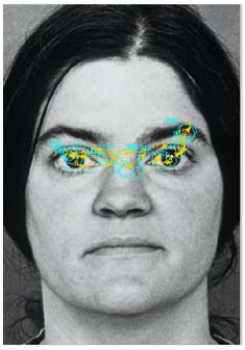
Godbee, K., & Porter, M. (2013). Attribution of negative intention in Williams Syndrome. *Research in Developmental Disabilities*, 34(5), 1602–1612.

Face Scanning

An eye-tracking study was also conducted at the WS Conference in 2007. This explored how individuals with WS process faces. Overall, the eyes did not capture the attention of WS individuals faster than controls. That is, WS and TD controls took a similar time period to make their first fixation to the eyes. However, once they looked at the eye region, the WS group spent significantly more time looking at the eye region of faces than TD controls. This suggests that WS individuals have difficulty disengaging their attention away from the eyes. There was variability in the WS face scanpaths, with some WS individuals (such as the one illustrated below), fixating completely on the eye region of the face, without scanning other important regions, such as the nose and mouth.



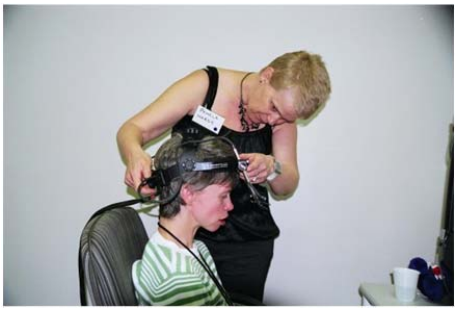
Typically Developing Control showing a typical 'upside down triangle' face scan path



WS Individual showing an atypical fixation on the eye region

When we looked at how well WS individuals recognise the basic emotions of happiness, sadness, anger, and fear, the emotion recognition abilities of WS individuals in this study were, for the most part, similar to TD individuals of the

same mental age, but lower that the emotion recognition abilities of same-age peers. There were two exceptions: i) WS individuals were similar to same-age peers in recognising happy expressions and ii)WS individuals, overall, showed a particular deficit in recognising angry faces relative to mental age matched controls. Importantly, emotion recognition abilities varied considerably amongst the WS group, and emotion recognition abilities were not significantly related to level of IQ.



Porter, M.A., Shaw, T., & Marsh, P.J. (2010). An Unusual Attraction to the Eyes in Williams-Beuren Syndrome: A Manipulation of Facial Affect while Measuring Face Scanpaths. *Cognitive Neuropsychiatry*, 15(6), 505-530. doi:10.1080/13546801003644486

Other Research Findings 2008-2014

From 2008 to 2014, we grew our research database from 50 WS individuals to over 100 individuals with WS:

- Age 2 ½ to 51 years
- 47% Male
- 64% right handed, 22% left handed, 11% ambi-dexterous, 3% unestablished

From 2010-2013, Melanie and her doctoral student, Gabrielle Brawn, collected data on daily independence and literacy skills. The main findings are outlined below.

Daily Independence:

- Living arrangements: 93% lived with their family, 5% in a group home, 1% lived independently, 1% lived with a romantic partner
- 40% of adults were in supported employment
- There was extensive variability in adaptive functions (or level of daily independence)
- Level of daily independence was significantly related to family culture and attitudes, with families that encouraged independence and intellectual growth being more likely to have a WS son/daughter with higher levels of independence in daily living skills.

- Level of daily independence was not significantly related to IQ

Brawn, G. & Porter, M.P. (In Press). Adaptive functioning in Williams syndrome and its relation to demographic variables and family environment. *Research in Developmental Disabilities.*

Brawn and Porter (Submitted). "Adaptive Functioning in Williams Syndrome: A Systematic Review", *Journal of Disability, Development and Education.*

Reading Skills

Gabrielle also looked in detail at reading in her cohort. The main findings were as follows:

- Reading abilities varied widely in WS
    - 20% were reported to be extremely poor readers
    - 19% were reported to be average readers
- There are many causes of reading disability in the typical population, this was also true of individuals with WS. Some WS individuals had problems with:
    - Letter to sound rules
    - Sequencing of letters within words
    - Visual memory of whole word patterns

- While IQ was not found to be a determining factor in reading performance, several cognitive skills known to be related to reading ability in typically developing individuals were found to be predictive of reading performance, such as working memory (the ability to hold and manipulate information in mind).
- Higher reading ability was found to be associated with increased outcomes in written and expressive communication skills and community living skills, such as ability to catch public transport, highlighting many potential benefits of developing reading abilities in WS.

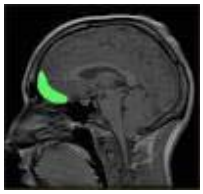
Brawn, G. & Porter, M.A. (Submitted). Functional Basic Reading Skills in Williams Syndrome", Annals *of Dyslexia*.

Structural Brain Imaging

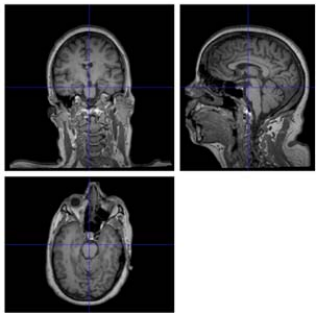
Melanie and her colleagues, Prof. Caroline Rae (Neuroscience Research Australia) and Prof. Mark Williams (Macquarie University) have also been working on two brain imaging studies in WS, one looking at brain structure and connectivity and the other, more recent study, looking at brain function.

For the structural brain imaging study, findings are very preliminary, but suggest significant differences in volume in:

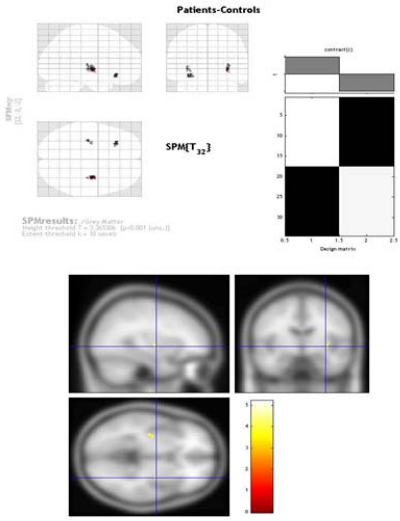
- Insula – involved in perception, motor control, emotion and cognitive processing
- Left Orbito-frontal gyrus – relates to disinhibited behaviour, decision making and adaptive learning and has also been implicated in ADHD



Orbito-frontal gyrus



An example WS structural brain scan



Putting it all together: Genetics, Cognition and Social Abilities

In a recent study, Porter et al. compared the cognitive, social and mental health functioning of individuals with the standard ~1.6Mb deletion versus those with the larger 1.8MB deletion.

Findings suggested similar levels of overall intellect (IQ) amongst the groups, as well as similar levels of daily independence and verbal abilities.

In contrast, individuals with the larger 1.8Mb deletion showed greater levels of impairment in:

- visual spatial difficulties
- social reasoning
- sticky thinking (obsessions, getting stuck on thoughts)
- behaviour difficulties
- depression

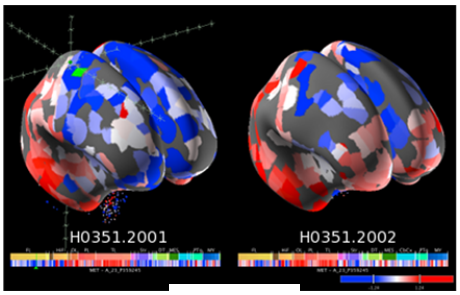
Following the above, Melanie and her team have expanded their multi-disciplinary research to include comprehensive neuropsychological assessment, brain imaging and neurological examinations to compare WS individuals with the typical deletion to those with atypical deletion sizes. This work has continued at the 2014 conference.

Porter, M., Dobson-Stone, C., Kwok, J., Schofield, P., Beckett, W., & Tassabehji, M. (2012). A role for transcription factor GTF2IRD2 in executive function in Williams-Beuren syndrome. *PLoS One*, 7(10), e47457. \

New Research Directions: 2014 and beyond

A key focus of Melanie's research is to look at individual differences amongst people with WS, including differences at genetic, mental (psychological, cognitive, academic, social) and neurological levels. Ultimately, the idea is to look at how genes within the WS region affect brain development and how this then leads to changes in cognitive and mental functioning. A key focus in the future will also include ***interventions*** to reduce the impact of psychological, cognitive, motor, academic and social difficulties in WS and related disorders. In particular, at this stage we do not have research evidence to show one way or another whether current treatment methods are effective for individuals with WS.

Genes



Brains

Thinking

Behaviour

Emotions

Real world functioning

Take Home Messages for Parents:

- Regular psychological monitoring is essential
- Maximise education support → do not use IQ as a sole determinant of education needs
- Encourage daily independence
- Provide opportunities for social engagement, environmental enrichment and growth, especially in adulthood
- There is a lot of variability in WS
    - Comprehensive assessment of strengths and Weaknesses is essential
    - Individually tailored intervention is required
- Just because your child has a low IQ does not mean that they
- cannot learn to read
- Full genotyping is important
- Multi-disciplinary research participation is extremely beneficial

3D facial imaging at the Williams Syndrome Conference in Sydney 2014

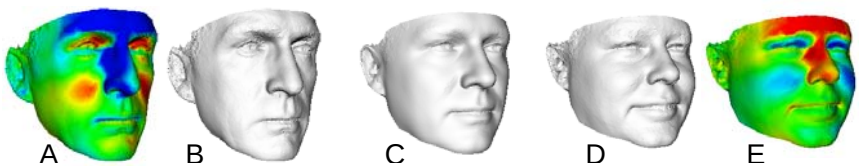
Seven years ago at the 2007 Williams syndrome conference in Sydney, I brought a special 3D camera to take photographs of individuals attending who had Williams syndrome and also some of their family members. Dr May Tassabehji from Manchester University in the UK, Dr Melanie Porter at Macquarrie University and I have been analysing those images in connection with behavioural and genetics data. This September, I returned to Sydney with Dr Tassabehji to add more images to our study. The big difference this year was that instead of lugging a 40 kg camera from London to Sydney that looks like the one below left (Fig 1A), I came with a portable camera that looks like the one on the right (Fig 1B).

A B

Figure 1: older and newer 3D cameras used to study 3D face shape

This was the first time I had used this camera other than on a few colleagues at work or on friends and family. It was very convenient as it is light and simple to use. However, it showed that it has some teething problems and not all of the images came out as well as they would have if I had used the old camera. Those of you who had your image taken this year will have noticed that I had to take three shots of your face – from the left, from front on and from the right. In about 30% of cases, people moved slightly or changed their facial expression in between shots and so it was not possible to get a uniform view for all three and the 3D photo either failed or was of inferior quality. However, there were still sufficient good quality images to make the trip worthwhile.

During my presentation at this year's conference, I was able to describe some of the analyses I have undertaken with the set of images captured in 2007. One aspect I was particularly keen to talk about was the discovery we made last year that the face shape of people with Williams syndrome can have a surprisingly simple mathematical relationship to the face shape of people who have a duplication of the region of chromosome 7 that is typically deleted in Williams syndrome. This involves inverting the shape of a face to be smaller/larger where it is larger/smaller than average. For example, my face looks like Fig 2B and Fig 2A shows it coloured green where it agrees with the norm for men of my age (Fig 2C), red where it is smaller and blue where it is larger than the norm. Figure 2E shows the inversion of my face, now red/blue where my face was blue/red in Figure 2A. Finally, Fig 2D shows the inversion of my face shape compared to the norm (Fig 2C).



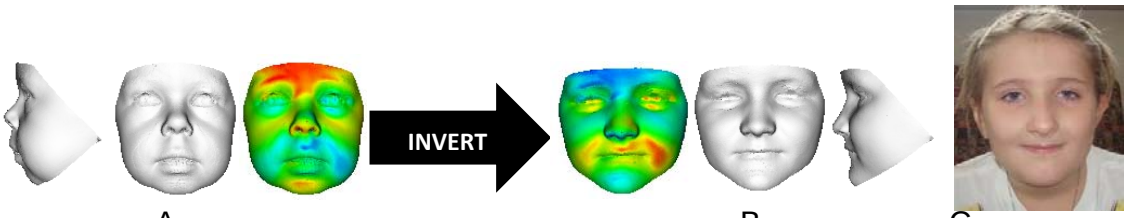
A B C D E

original norm inversion

Figure 2: inversion of face shape

So whereas my face is relatively long and thin compared to average, the inversion is shorter and wider (and maybe heavier and older looking!).

Now, if we invert the face of a child with Williams syndrome (Fig 3A) in a similar fashion using an age-sex matched norm we get a face shape (Fig 3B) that is very close to the face shape of children known to have a duplication of the Williams syndrome region (Fig 3C) and in the published literature.



Velleman & Mervis, Perspect Lang Learn Educ. 2011 , 18(3): 108–116

Figure 3: inversion of face of child with Williams syndrome

You are probably wondering what this means and if it is at all relevant to Williams syndrome. Well, for some time clinicians and scientists have commented that individuals with Williams syndrome, with a deletion of 7q11.23, have some opposite characteristics to those with a duplication of 7q11.23. The suggestion is that some of the genes that are lost or duplicated are what is known as dosage sensitive, i.e. the number of working copies an individual has can reduce or increase certain characteristics, for example personality and behaviour and even physical appearance. For example, children with Williams syndrome are unusually friendly, have a short upturned nose and often a small chin. Children with a duplication of 7q11.23 appear to be less overtly friendly and have a longer nose and more prominent chin. It turns out that we could show a similar result for more genetic conditions associated with loss or addition of certain genes on other chromosomes. A detailed description was published in a journal earlier this year (details below). We now look forward to analysing the new images to identify yet more interesting aspects of Williams syndrome and the genes that are involved, and hopefully in the not too distant future we will return to Sydney to describe them.

Peter Hammond

Reference

Opposite effects on facial morphology due to gene dosage sensitivity. P Hammond, S McKee, M Suttie, J Allanson, J-M Cobben, SM. Maas, O Quarrell, ACM Smith, S Lewis, M Tassabehji, S Sisodiya, T Mattina, R Hennekam. Human Genetics, 2014, 133:1117-1125.

WS families WS Conference, Macquarie University 22nd September 2014

Research Findings from the 2014 WS Conference will be posted to you in 2015 once the data collection has been completed!

A HUGE THANK YOU TO FAMILIES AND TO OUR RESEARCH FUNDING SUPPORTERS:

Australian Rotary Health
www.australianrotaryhealth.org.au

MACQUARIE UNIVERSITY
SYDNEY ~ AUSTRALIA

APEX AUSTRALIA
Apex FOUNDATION

WILLIAMS SYNDROME
Australia Limited