Society for the Study of Behaviour Phenotypes (SSBP) 21st International Research Symposium 2018.

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Abbreviations:_NBPSA (Neurodevelopmental and Behavioural Paediatric Society of Australia), FMRP (Fragile X Mental Retardation Protein), FXS (Fragile X Syndrome), ID (Intellectual Disability), PWS (Prader Willi Syndrome), ASD (Autism Spectrum Disorder), AS (Angelman Syndrome), DS (Deletion syndrome), WS (Williams Syndrome), TSC (Tuberose Sclerosis Complex), PKU (Phenylketonuria).

The meeting was in Melbourne, 28-30th August hosted by Honey Huessler. The first two days were devoted to research papers with the educational day shared with the Neurodevelopmental and Behavioural Paediatric Society of Australia (NBPSA) on the final day.

The first keynote address was by David Godler, Group Leader, Cyto-Molecular Diagnostics Research Group of the Murdock Children's Research Institute (MCRI) in Melbourne on the molecular model and clinical aspects of FMRP in FXS, highlighting the significance of mosaicism. Mosaicism is a complex phenomenon which can have a major impact on diagnosis and research into rare genetic syndromes. It is a common cause for delayed or absent diagnosis, and the degree of mosaicism can vary over time in one individual. Mosaicism may well have diluted the efficacy of the Novartis trial of AFQ056 in FXS. It remains unclear how low is the threshold above which mosaicism becomes meaningful. He presented an overview of the molecular pathology in this syndrome. Although targeted treatment in mice with FXS correct the phenotype, this is unsuccessful in humans. One possible reason is that the mice are clones, whereas human pathology varies immensely, including as a result of mosaicism. Current studies are examining the prevalence of FXS and chromosome 15 imprinting disorders (PWS & AS) in 100,000 and 75, 000 newborns respectively.

Claudine Kraan from the same MCRI research group presented on FMRP allele size distribution in 35,000 males and females. Firstly a new group has been identified with an abnormally low number of CGG (cysteine, guanine, guanine) repeats, less than 27, and this may be associated with some disorders. This low count is found in 1:5 males and 1:3 females. The grey zone of 45-54 repeats does not in itself appear to be associated with ID, and some studies that show such an association may well have included undetected full mutations given sensitivity problems with current diagnostic tests, and the issue of mosaicism. CGG repeats greater than 80 are associated with FXTAS (Fragile X-associated tremor/ataxia syndrome) and FXPOI (Fragile X-associated primary ovarian insufficiency), but not with ID. Some individuals in the pre-mutation range are shy and awkward, but ID in this range may be associated with a second 'genetic hit'. She reported on a study of 19,000 referrals to the Victorian Genetics Service, which were compared with two independent cohorts from the general population. There was no association between expansions in the grey zone and pre-mutation zones, and developmental delay.
(https://www.youtube.com/watch?v=iFNUOZXcv-M)

Emma Baker also from the same MCRI research group presented on FMRP mRNA in blood as a predictor of intellectual functioning and autism severity in FXS. She noted in females 22-50% have an ID, and 16-20% have ASD. In males 100% have ID and 30-55% ASD. Lower IQ is the driver for the higher rates of ASD in males more than females. 60% of males and 100% of females still have some FMRP depending on IQ, i.e. mRNA is not completely silenced. She presented a study of 125 individuals (28% female) with FXS, which showed that FMRP mRNA levels in blood were strongly associated with IQ in males but not females, and with symptoms of ASD in females but not males. This discrepancy remains unexplained.

Randi Hagerman, Director of the MIND Institute, UC Davis, presented the results of a controlled trial of sertraline in children between 2 and 6 years with ASD but without FXS. A previous trial showed efficacy in FXS. Sertraline stimulates BDNF (brain-derived neurotrophic factor) which improves neuronal connectivity and can lead to improvements in expressive language and a reduction in reactivity. 58 children were recruited, 4 with identifiable genetic syndromes. 6 patients discontinued, and the remainder were treated with 2.5 -5mg sertraline daily depending on age. A number of individuals did well but the overall results failed to reach significance, possibly a consequence of the het-

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erogeneity of ASD.

Stephan Huijbregts a neurodevelopmental psychologist from Leiden presented a study of the impact on metabolic control of early treatment of PKU with tetrahydrobiopterin (BH4). BH4 is a cofactor of phenylalanine hydroxylase (PAH) which is deficient in PKU. PAH is required for the conversion of phenylalanine into tyrosine. Subjects had been treated early with a PKU diet. He noted that even in early treated PKU IQ was in the low normal range and there were higher rates of executive dysfunction, depression and anxiety, depending on phenylalanine levels. The addition of BH4 produced small but significant differences to Health-Related Quality of Life measures in adults but not children. (This medication is only on the Australian PBS for BH4 deficiency and costs >$5000/month otherwise.)

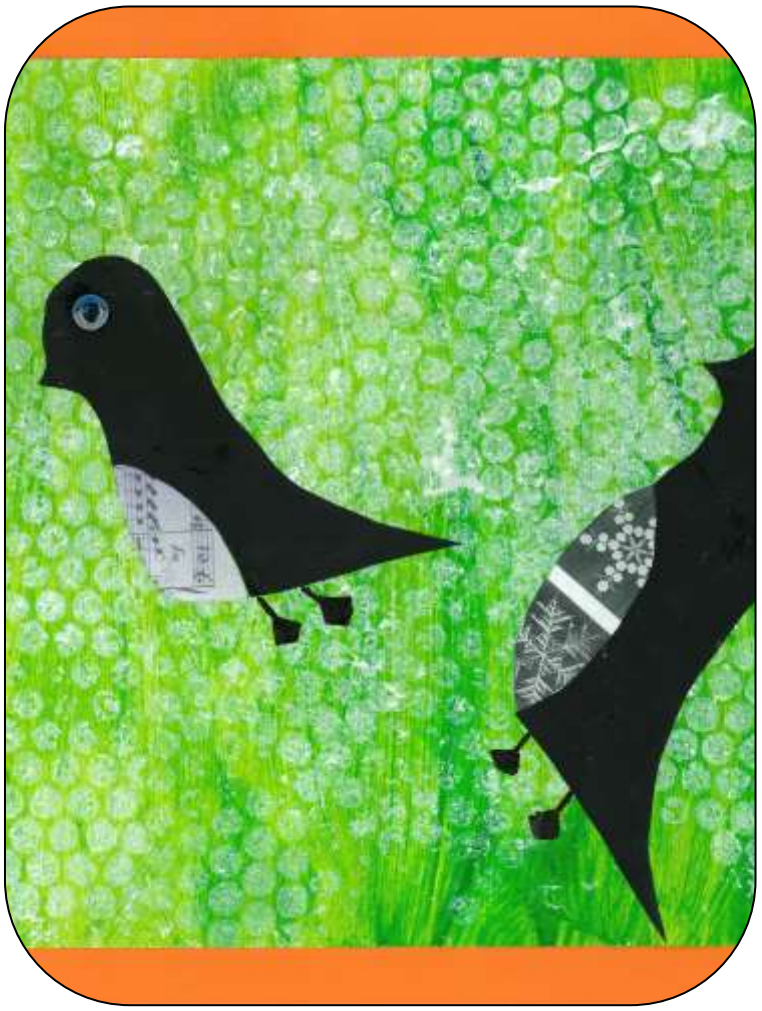
Flora Tassone from UC Davis presented on Global Methylomic Profiling in children with ASD. She noted that methylation is a common epigenetic modification of DNA. The study involved 44 age-match participants with and without ASD, and found significant numbers of altered methylation in 47 genes in the ASD group, mainly hypermethylation with some hypomethylation. She noted the potential to contribute to diagnostic classification and possible therapies.

The second keynote address was by Tony Simon from UC Davis on the impact of cognitive-affective interaction on risk and protection for psychosis in 22q11.2 DS (VCFS). These individuals have IQs varying between 55 and 100. ADHD is found in 20-50%, typically the inattentive type. ASD is frequently diagnosed on the ADI given to parents but not on the ADOS. Anxiety is seen in 50-60% and schizophrenia in perhaps 20%, with typical onset between the ages of 18 and 35. He noted that while IQ is predictive of adaptive function in neurotypicals, anxiety is far more predictive in those with this syndrome. He noted that anxiety may be due to ‘misattribution of salience of environmental stimuli’, leading to high levels of ‘allostatic cognitive load compared to capacity’. Affectively laden distractions impair attention excessively in this syndrome. The apparent ASD often diagnosed appears to resemble a combination of anxiety and avoidance, and most of these individuals are very socially motivated. High anxiety in early adolescence in probably a predictor of the later development of psychosis. This hypothesis is the focus of a current longitudinal study. (https://www.youtube.com/watch?v=VVcvPkUSoVA)

Tony Simon again presented on 22q11.2 DS, comparing various measures of ASD in 17 children with this syndrome compared to a matched group of children with idiopathic ASD. There were divergent scores on language, some overlap on scores on ADOS items, and qualitative differences in social impairment. He speculated that ASD in this population could represent a psychotic prodrome.

Linda Campbell from Newcastle presented on emotional dysregulation in 22q11.2 DS. She noted that these individuals have higher scores than typicals on anger and aggression, and 7-14% are diagnosed with disruptive disorders. A cross-sectional sample of 129 subjects compared with 116 typical children aged 4-22 was assessed with a range of measures, showing 50% had significant problems with emotional control compared to 8% of typicals. Emotional dysregulation was significantly predictive of behavioural problems including aggression.

Donna McDonald-McGinn from Philadelphia Children’s Hospital presented on language decline in 22q11.2



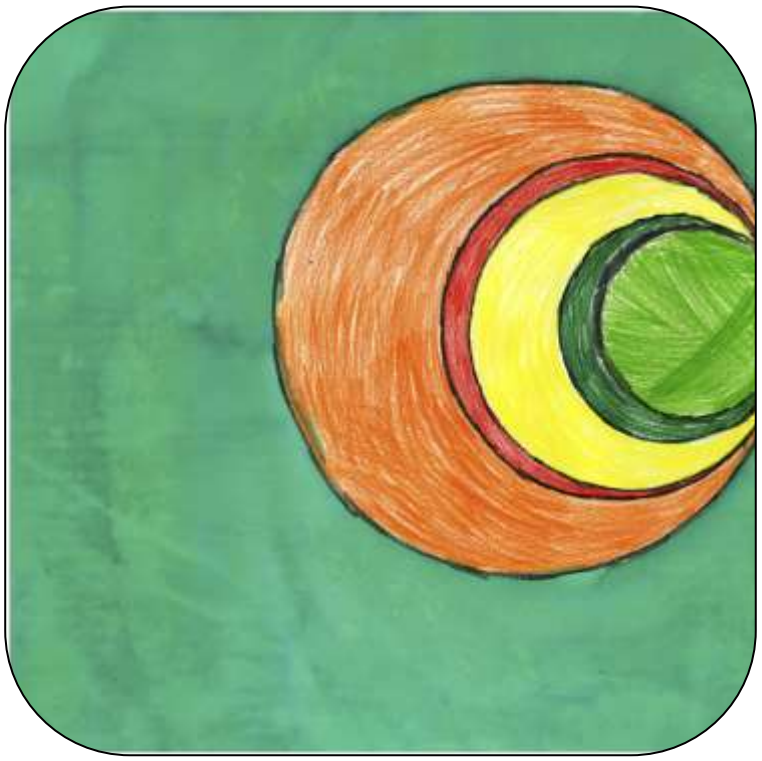
DS. Schizophrenia is reported to follow a decline in cognitive and language scores in this syndrome. A retrospective chart review of 730 children up to the age of 21 was performed. Significant declines in cognitive functioning occurred in many children before the age of 10, including a striking decline in language scores. FSIQ declines as VIQ falls to match PIQ. Further work to determine any association between the degree of decline and the subsequent onset of schizophrenia is planned. She also noted that some individuals with this syndrome develop early onset Parkinson's disease.

Pat Howlin from Kings College London described efforts to identify what interventions work with which children with ASD. ASD is clearly heterogeneous yet most research focuses on group outcomes. She explored factors predictive of treatment response as opposed to variables related to prognosis on autism more generally, in two large groups of children. Interventions tended to produce significant group effects, with variability of response within groups. None of the variables identified reliably distinguished responders and non-responders, illustrating the complexity of the field.

Lauren Lawson from La Trobe University Melbourne described gender differences in internalising psychopathology in young adults with ASD. The limited studies in this area typically find little difference in the prevalence of anxiety and depression between males and females, but her study of 111 subjects found the same overrepresentation of anxiety and depression in females with autism as is found in neurotypicals. This correlated with a significantly higher use of emotional regulation involving suppression in females than males.

Melanie Porter Director of the Centre for Research in Atypical Neurodevelopment at Macquarie University described the complex gene and environmental contributions to the phenotype of WS. She noted that phenotype can be defined as the observable expression of the interaction of genotype and environment. WS is due to a 7q11.23 deletion which typically involves the loss of 26, occasionally 28 genes. While there is significant heterogeneity of expression, individuals are typically hypersocial, empathic, musical, with hyperacusis, poor emotional regulation and a high frequency of mental illness, especially ADHD, Generalised Anxiety Disorder, depression and specific phobias. They have a mild to moderate level of ID, significant executive dysfunction, and a higher frequency of cardiovascular and connective tissue disease. They exhibit a positive cognitive bias, and tend to focus on eyes more than the whole face compared to neurotypicals. There are widespread changes in brain structure with loss of volume and connectivity. 34-40% of children with WS take stimulants, and 26% of adults take psychotropic medication.

Liz Pellicano from Department of Educational Studies, Macquarie University, Sydney described the need for autism researchers to involve patients and families to a much greater extent. There has been a surge in publications on autism since 2000 from 500 to 3500 papers per year, but it is not clear that this work has made any difference to the lives of people with autism and their families. Most of them feel that higher rates



of anxiety and depression are due to their experience of others as a result of stigma, exclusion, the pressure to be normal and a failure of empathy by neurotypicals. People with autism do not adapt to stimuli as much, and tend to see the world more accurately and less biased by previous experience. The need to involve subjects and their families in research was a theme that recurred throughout the conference.

Anna Jansen paediatric neurologist from University Hospital Brussels described the top fifteen research priorities in TSC derived from focus groups and interviews with patients and caregivers. The major problems identified were refractory epilepsy, disfiguring skin lesions and TAND (TSC-associated neuropsychiatric disorders). This was the second presentation highlighting the need to involve individuals with genetic disorders themselves in research.

Continuing this theme, Dawn Adams from the Autism Centre of Excellence Griffith University Queensland presented on parent thoughts on clinical trials for children with a number of rare genetic disorders. Many were surprisingly keen to participate in trials of approaches that have only previously been researched in mice. Most were keen to see the personality of their children not affected by any treatment, and attitudes to 'cure' varied. Parents of individuals with 22q11.2 wanted research on mental illness, and parents of those with AS wanted research on speech and communication.

Rachel Cvejic from 3DN, University of NSW Sydney presented preliminary data on the use of 'big data' in behavioural phenotype research. Linkages are now possible between data on presentations to EDs, hospital admissions, ambulance trips, and births and deaths. These linkages can create cohorts by diagnosis. A retrospective study of 492 people with AS and 3570 with Down Syndrome who were admitted to New South Wales hospitals over a 14 year period was conducted. Individuals with AS were five times more likely to be admitted for accidental injury than those with DS or neurotypicals. Rates for interpersonal violence and falls were much higher for AS. There are still big gaps in the data, which relies on the accuracy of coding. ICD10 lumps multiple rare copy number variations together.

Rachel Royston from Birmingham presented on risk factors for psychopathology in WS, FXS and PWS. Affective and anxiety disorders are much more common in FXS, specific phobias in WS and FXS and psychosis in PWS. Sensory hypersensitivities predict anxiety. There was no association with age, and none of the variables studied predicted psychopathology in FXS.

Laura Groves from School of Psychology University of Birmingham presented on anxiety disorders in Cornelia de Lange and FXS. Both conditions have high rates of anxiety disorders. This study found a disconnection between subjective experience and diagnosis reflective of the lack of sensitivity of the diagnosis of anxiety disorders in this population. DSM 5 is particularly insensitive, given the excessive reliance on subjective phenomena in diagnostic criteria.

Kylie Gray from the Centre for Developmental Psychiatry & Psychology, Monash University presented a comparison of the efficacy of community-based parent intervention for children with and without ASD. 365 families who took part in the Stepping Stones Triple P program were studied. The diagnosis of ASD was based on parent report only. The children with ASD had significantly higher rates of behavioural and emotional problems at all time points compared to those without, but both groups demonstrated significant decreases in these problems after treatment. This program relies on parent education about behavioural management. Benefit was maintained at 3 and 12 month follow ups. Financial hardship was controlled for and the average IQ of the children was 63.

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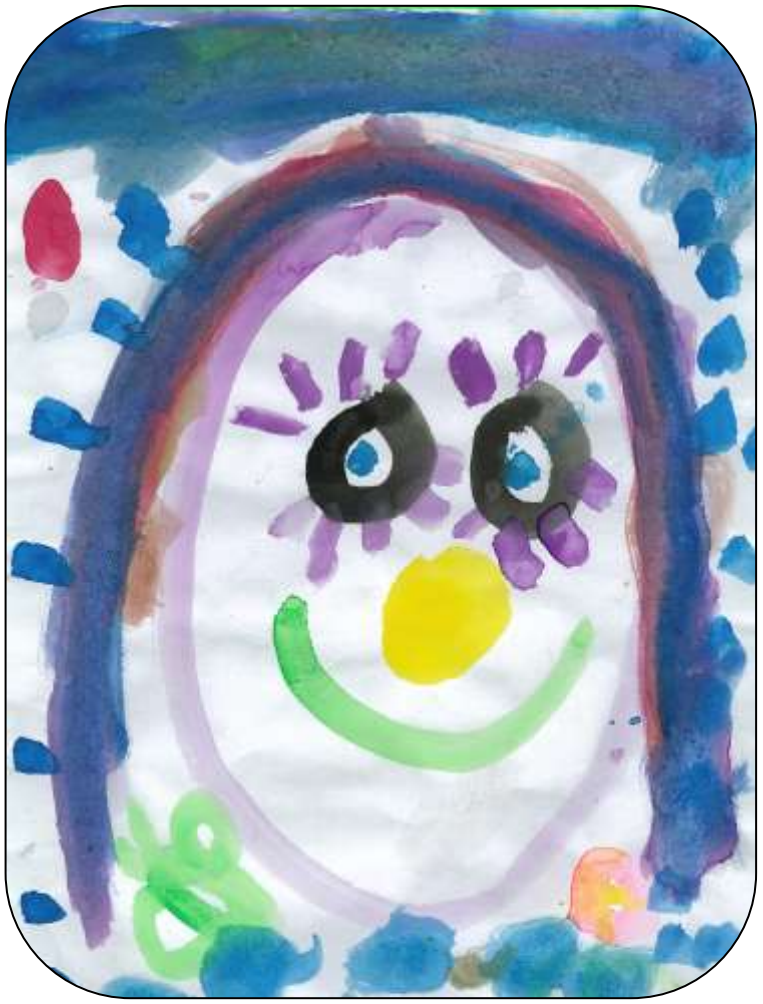
“School non-attendance is 50% more common in intellectual and developmental disorders”

Effie Pearson from the School of Psychology, University of Birmingham presented on communication in AS, a disorder caused by a deletion or alteration of the gene UBE3A (Ubiquitin-protein ligase E3A), which occurs in 1:12000-20000 births. Non-deletion forms of AS (ie. uniparental disomy or imprinting problems) had better communication skills than those with a deletion. Speech is absent or severely impaired across this spectrum however regardless of cognitive ability. Spoken language skills dissociated from other communicative abilities, suggesting specific involvement of this gene in speech production. Alternative communication aids are therefore likely to be more effective in this population.

Megan Tones from the Mater Medical Research Institute, Brisbane presented on developmental milestones in AS using data derived from the Global AS Registry, a Queensland initiative. There are 700 individuals on the register, and 75% have the deletion form. Only 20% are older than 18 years. There are more mutations of UBE3A than cases of uniparental disomy in this group. There was a wide range of ages in meeting standard developmental milestones, which were typically more delayed in those with the deletion form than other subtypes.

Bruce Tonge, Emeritus Professor of Psychiatry, Monash University gave the Tom Oppe lecture on school non-attendance in young people with developmental disabilities. He described the evolution of his understanding and the shift in name from school refusal to school non-attendance. This can be authorised, ie. agreed upon at all necessary levels including the Education Department, and unauthorised, a local initiative of either school or families. He identified four categories – refusal, associated with anxiety and depression; truancy, associated with disruptive behaviour disorder; withdrawal by parents as a result of parental need; and exclusion by the school, either local, inappropriate and unlawful, or formal and sanctioned by the Education Department. There is no good information on long-term outcomes which are likely to be poor. Problematic non-attendance is 50% more common in intellectual and developmental disorders than in neurotypicals, and 300% more common when persistent. About 10% of students with ID experience exclusion from schooling. A surprising figure was the number of days missed as a result of attendance at medical appointments. Children with ASD, WS and PWS had an increased prevalence of non-attendance whereas those with Down Syndrome and FXS had a reduced prevalence. Authorised non-attendance was particularly prevalent in ASD. 45% of parents struggled to overcome their children’s resistance to going to school. A high prevalence of this problem was also found in a study from Warwick, UK.

Petrus de Vries, Professor of Psychiatry, University of Cape Town presented on TSC-associated neuropsychiatric disorders (TAND). TSC affects 1:6000, and 30% are inherited in an autosomal dominant pattern, with males equalling females, and the rest new mutations. Mortality under 5 years has plummeted in the last 25 years but the level of ID has not changed. The TSC1 or hamartin gene on chromosome 9 and the TSC2 gene tuberin on chromosome 16 combined to form a complex which inhibits mTOR (mammalian or mechanistic target of rapamycin) which regulates cell growth. The failure of this complex to form in TSC results in much higher levels of mTOR, which cause the overgrowth and tumours seen throughout the body. Sirolimus and analogues inhibit mTOR and shrink tumours, as well as improving seizures, and are now on the Pharmaceutical Benefits Scheme for selected indications in this

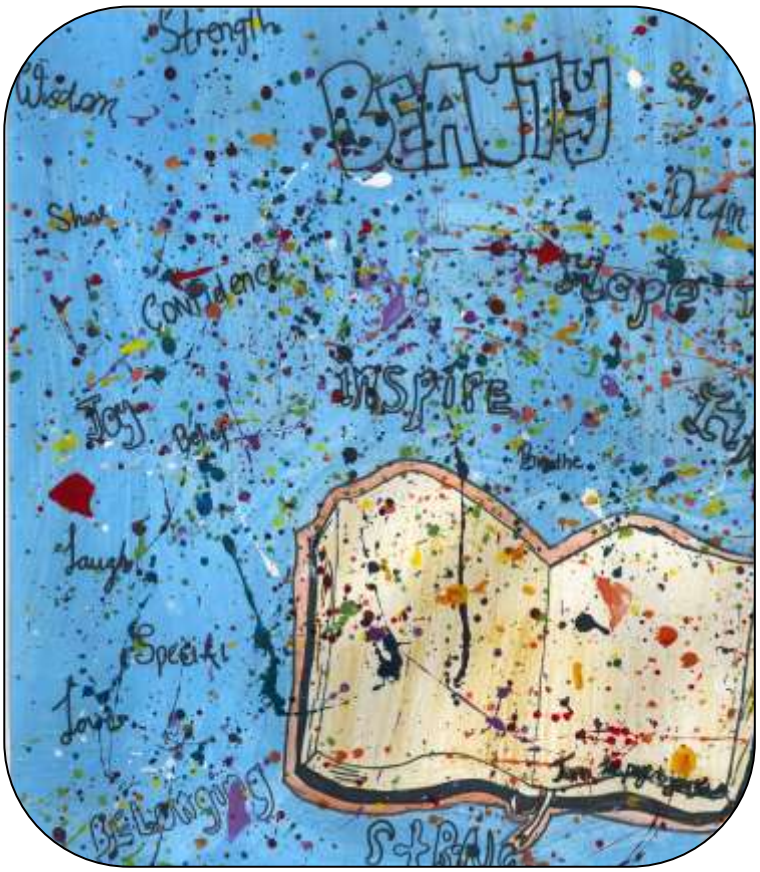


condition. There are numerous neuropsychiatric complications including ASD, ADHD, learning disorders, executive function disorders, depression and anxiety, as well as ID. There is no increase in psychotic illnesses. There is a freely available fifteen minute TAND checklist in fifteen languages, and the aim is to have all individuals with TSC screened annually, in order to correct the pervasive underdiagnosis of TAND around the world.

Honey Heussler from Child Medical Research Centre, University of Queensland presented on medical cannabinoids. She described Scott's parabola, developed to describe the phases through which new surgical treatments pass, from non-use, to excessive hype, to peak use, to the recognition of problems and eventual disuse. Cannabinoid usage is now in the upwards slope of this parabola. The most common compounds are cannabidiol and THC. Different brands of medicinal cannabis have various ratios of these two compounds. It is used in MS, oncology and possibly in Parkinson's disease. Cannabidiol has multiple sites of action. 30-50% of cases of refractory epilepsy respond although some show worsening. It may be useful in lessening anxiety in FXS. There is currently insufficient available information to recommend its use, although many parents of individuals with ID are already obtaining various compounds.

ACT paediatrician Felicity Williams presented on her experience of having a four year old child with AS. Gross motor delay was evident at six months leading to diagnosis. She described the inevitable need to socialise with other parents who understood the issues involved, and with whom there was frequent contact during the different therapies required. She described the multiple appointments and associated costs, and the need to celebrate small achievements. Her personal experience has helped her understand the perspective of parents with children with severe ID, and helped her explain to these parents the current deficit model of funding, which requires parents to emphasise their child's weaknesses rather than their strengths and attributes. It has helped her recognise both the value and burden of having a child with ID in a family. She noted that five gene-based therapies for AS are entering development.

Stewart Einfeld from Sydney University presented on behavioural phenotypes in PWS, WS and 22q11.2. He focused especially on individuals with PWS. Emotional ability is much lower than IQ, which is typically in the mild to average range of ID. If they are upset they regress quickly, and are very egocentric. Skin picking is common and NAC (N-Acetyl Cysteine) and topiramate are occasionally helpful. They perseverate, check and



hoard, but there are none of the classic cognitive associations seen in OCD, the behaviour is not ego dystonic, and these behaviours do not respond well to OCD medication. 10-30% develop psychosis, at seven times the rate in UPD (Uniparental Disomy) compared to deletions, with typical onset before 40 and as young as 9. The peak incidence occurs in late adolescence, and is typically relapsing-remitting but occasionally chronic. Depression is more common than psychosis and responds to standard treatment. Temper outbursts including rage attacks are a major problem, which can last until exhaustion sets in. No medication has been shown to be helpful. There is a lack of functional oxytocin but trials of oxytocin have been ineffective or counterproductive. There are trials of the longer acting carbitocin and mindfulness underway. Tantrums diminish over the age of 30. There are deletions of the COMT gene in 22q11.2. The psychotic illness looks identical to schizophrenia and is often fairly treatment resistant. Anxiety is common and treatment follows the usual lines. WS individuals exhibit high levels of anxiety, including specific phobias which respond to SSRIs. Hyperacusis responds to avoidance of stimuli and earplugs. They have low anxiety about strangers and are indiscriminately positive towards them. There is a very high incidence of childhood sexual abuse.

There were numerous poster presentations of a high standard, covering a range of syndromes. The next conference will be in Birmingham, UK from the 4th to the 6th of September 2019.