

**HOPES, FEARS AND BELIEFS ABOUT CLINICAL TRIALS FOR CHILDREN WITH ANGELMAN SYNDROME, 22Q11.2 DELETION SYNDROME AND OTHER RARE GENETIC DISORDERS**D. Adams,<sup>1,2</sup> E. O'Reilly<sup>3</sup> & H. Heussler<sup>3,4</sup><sup>1</sup> Autism Centre of Excellence, Griffith University, Brisbane, Queensland, Australia<sup>2</sup> Griffith Institute of Educational Research, Griffith University, Brisbane, Queensland, Australia<sup>3</sup> Children's Health Queensland, Queensland, Australia<sup>4</sup> Mater Research Institute, University of Queensland, Brisbane, Queensland, Australia

**Background:** The rapid growth in genomic medicine has led to advances in potential treatments for a number of rare syndromes. However, little is known about what parents of children with such syndromes think and feel about these trials and their priorities for treatment. **Methods:** Parents of 89 children with Angelman ( $n = 42$ ), 22q11.2 deletion syndrome ( $n = 20$ ) and other syndromes ( $n = 27$ ) completed an online survey. Questions asked about their knowledge and perspectives on clinical trials and the specific areas they feel should and should not be targeted by treatments. **Results:** The majority (91%) felt that clinical trials aiming to reduce symptoms associated with their child's syndrome were positive, but there were significant differences between groups in the proportion that felt that such trials should be aiming to 'cure' their child's syndrome ( $\chi^2(4) = 28.9, P < .001$ ). Although less than half of parents reported feeling at least 'moderately' confident in their knowledge about clinical trials, nearly half of the parents reported being keen to take part in clinical trials, even if the treatment had not been trialled in humans. Behaviour and IQ were identified as priority target areas by 33.3–45% and 15–19% of parents (respectively) across all three groups. However, other target areas were syndrome-specific, with mental health being identified as a priority by 50% of the 22q11 group and speech/communication by 73.8% of the Angelman group. Almost one-third identified personality as the one characteristic they would not want to be changed. **Conclusion:** This expands the limited knowledge on parent's perceptions and priorities for treatment trials. Parents of children with rare genetic syndromes are motivated and keen to take part in trials to reduce the symptoms of their child's syndrome, despite potentially not being fully informed of what this means. It is important that researchers, clinicians and trial coordinators work together to increase parental knowledge prior to trials commencing.

**Keywords** 22q11, Angelman, parents, syndrome, trials**FMR1 MRNA IN BLOOD AS A PREDICTOR OF INTELLECTUAL FUNCTIONING AND AUTISM SEVERITY IN FRAGILE X SYNDROME: IS THERE A DIFFERENCE BETWEEN SEXES?**E. K. Baker,<sup>1</sup> M. Arpone,<sup>1,2</sup> S. Aliaga,<sup>1,2</sup> L. Bretherton,<sup>3</sup> M. Bui,<sup>4</sup> C. Kraan,<sup>1,5,6</sup> A. Allende,<sup>7</sup> C. Rogers,<sup>8</sup> D. J. Amor<sup>1,6,9</sup>& D. E. Godler<sup>1,6</sup><sup>1</sup> Cyto-Molecular Diagnostics Research, Murdoch Children's Research Institute (MCRI), Melbourne, Victoria, Australia<sup>2</sup> Faculty of Medicine, Dentistry and Health Sciences, Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia<sup>3</sup> Child Neuropsychology, Murdoch Children's Research Institute, Melbourne, Victoria, Australia<sup>4</sup> Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia<sup>5</sup> School of Psychological Sciences and Monash Institute of Cognitive and Clinical Neurosciences, Monash University, Melbourne, Victoria, Australia<sup>6</sup> Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia<sup>7</sup> Molecular and Cytogenetics Laboratory, INTA University of Chile, Santiago, Chile<sup>8</sup> Genetics of Learning Disability Service (GOLD service), Hunter Genetics, Newcastle, New South Wales, Australia<sup>9</sup> Victorian Clinical Genetics Service, Melbourne, Victoria, Australia

**Background:** Fragile X Syndrome (FXS) is a common single gene cause of intellectual disability and co-morbid autism spectrum disorder (ASD). FXS is caused by a large trinucleotide CGG expansion (>200 repeats) within the *FMR1* gene located on the X chromosome. FM alleles are associated with epigenetic changes that result in decreased production of *FMR1* mRNA and loss of the *FMR1* protein FMRP. Males with FXS typically present with a more severe phenotype compared to females; however, the biomarkers that underlie differences in both sexes have not

been defined. **Methods:** One hundred twenty-five individuals (28% female) with FXS aged between 1 and 43 years recruited from Australia and Chile participated in the study. The Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2) was used to assess symptoms associated with ASD, while cognitive functioning was assessed with the Mullen Scales of Early Learning (<3 years), and an age appropriate Wechsler scale [Verbal IQ (VIQ), Performance IQ (PIQ) and Full Scale IQ (FSIQ)]. **Results:** Genotype-phenotype analyses showed that *FMR1* mRNA levels in blood were strongly associated with FSIQ ( $P < .001$ ;  $n = 41$ ), VIQ ( $P = .029$ ;  $n = 41$ ) and PIQ ( $P = .002$ ;  $n = 43$ ) in males, but not in females (FSIQ:  $P = .394$ ,  $n = 24$ ; VIQ:  $P = .170$ ;  $n = 25$ ; PIQ:  $P = .438$ ;  $n = 25$ ). In contrast, *FMR1* mRNA levels were strongly associated with total Calibrated Severity Scores in females ( $P = .001$ ;  $n = .001$ ), but not males ( $P = .284$ ;  $n = 59$ ). **Conclusion:** This study shows that *FMR1* mRNA levels in blood are associated with symptoms of ASD in females and intellectual functioning in males with FXS. This dissociation by gender in the relationships between *FMR1* expression with type and severity of intellectual functioning and behavioural phenotypes warrants further study.

**Keywords** Autism, fragile X, *FMR1* mRNA, IQ**EMOTION DYSREGULATION IN 22Q11.2 DELETION SYNDROME**L. E. Campbell,<sup>1</sup> L. Swaab,<sup>1</sup> K. McCabe<sup>2</sup> & T. Simon<sup>2</sup><sup>1</sup> School of Psychology, Faculty of Health, University of Newcastle, Ourimbah, New South Wales, Australia<sup>2</sup> Department of Psychiatry and Behavioral Sciences, UC Davis School of Medicine, UC Davis MIND Institute, Sacramento, CA, USA

**Background:** Emotion regulation, also known as emotional self-control is the ability to regulate one's affect and emotions in response to environmental changes. Young people with 22q11.2 deletion syndrome (22q11DS) are at increased risk of psychiatric disorders associated with emotional dysregulation including anxiety. The current study aimed to investigate the rate of emotional dysregulation in young people with 22q11DS, and the associations with psychiatric comorbidity, compared with typically developing community controls. **Methods:** The cross-sectional sample included 245 children, aged 4–22 years, including 129 diagnosed with 22q11DS and 116 typically developing controls recruited from the UC Davis MIND Institute. Parents completed the Behavior Assessment System for Children, Second Edition Parent Rating Scale (BASC-2) and the Adaptive Behaviour Assessment System, Second Edition (ABAS-II). Participants completed the Wechsler Scales of Intelligence. **Results:** The 22q11DS sample had significantly higher scores on emotional self-control, indicating poorer ability to regulate emotions. More specifically, while only nine (8%) participants in the TD group had elevated or clinically significant problems with emotional self-control, this applied to 64 (50%) of participants in the 22q11DS group. Within 22q11DS group analyses identified no age or gender differences between the participants with emotional dysregulation and those in the typical range. A trend level effect indicated that the average IQ was higher (77 vs. 73) in the elevated group ( $P = .06$ ) although adaptive functioning was decreased compared to the group in the typical range ( $P = .013$ ). The group with the elevated emotional dysregulation had significantly higher rates of behavioural problems including anger control and aggressive behaviours. **Conclusion:** Emotional dysregulation is not only associated with anxiety but also leads to an increased risk of externalising behaviour such as anger control in this population. Emotional dysregulation is common among young people with 22q11DS should be a key target for interventions to improve behavioural outcomes in this population.

**Keywords** 22q11.2 deletion syndrome, aggression, anger control, emotion regulation**DOES ADMINISTRATIVE HEALTH DATA HAVE A PLACE IN BEHAVIOURAL PHENOTYPE RESEARCH?**

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**Background:** Behavioural phenotype studies typically involve direct observation or informant ratings of behavioural features associated with genetic syndromes. This study takes an alternative approach to investigate

whether administrative health data can be used to delineate syndrome-specific patterns of morbidity that may be linked to known behavioural phenotypes. As a group, people with intellectual disability experience higher rates of accidents/injuries than the general population; identified risk factors include epilepsy, impulsivity, absence of speech and high sociability. Here, we use hospital admissions data to determine the rates of different types of accidents/injuries among people with two distinct syndromes, Angelman syndrome (AS) and Down syndrome (DS), and compare these to the general population. **Methods:** A retrospective cohort study of people with AS ( $n = 492$ , 52% male) and DS ( $n = 3570$ , 53% male) aged 0–44 years who were admitted to hospitals in New South Wales (NSW), Australia, from 2002 to 2015. Direct standardised method was used to compare age-adjusted rates of hospitalisation for people with AS, DS, and the NSW general population. **Results:** Twenty-six per cent and 12% of people with AS and DS, respectively, were hospitalised for accident/injury from 2002 to 2015. The age-adjusted rate for admission for any accident/injury was five times higher in AS [8697/100 000 person years (PY)] than that in DS (1774/100 000 PY) and the general population (1847/100 000 PY). Rates of interpersonal violence and falls were also higher in AS (interpersonal violence = 3325/100 000 PY; falls = 2407/100 000 PY) than those for DS (interpersonal violence = 552/100 000 PY; falls = 489/100 000 PY) and the general population (interpersonal violence = 1743/100 000 PY; falls = 1844/100 000 PY). **Conclusion:** Our findings show a double dissociation between admission rates for specific types of accidents/injuries between two genetic syndromes with contrasting behavioural phenotypes, with important implications for prevention planning. This provides preliminary evidence of the potential utility of administrative health data in the context of behavioural phenotype research.

**Keywords** accidents, Angelman syndrome, Down syndrome, injury, hospital admissions

#### A COMMUNITY-BASED PARENTING INTERVENTION FOR PARENTS OF CHILDREN WITH A DISABILITY: COMPARISON OF EFFECTIVENESS FOR CHILDREN WITH AND WITHOUT AUTISM SPECTRUM DISORDER

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**Background:** Among children with intellectual disabilities, children with autism spectrum disorder (ASD) have higher rates of behaviour and emotional problems than those without ASD. Parent training programmes, such as Stepping Stones Triple P (SSTP), have been shown to reduce child behaviour and emotional problems. This study aimed to evaluate whether the community-based SSTP programme produced comparable outcomes for children with and without ASD (i.e. whether having ASD moderated the treatment outcome effect).

**Methods:** A subsample of 365 families who took part in the Stepping Stones Triple P (SSTP) programme was analysed, including children with an intellectual or developmental disability aged 2–10 years. Parents reported whether their child had been diagnosed with ASD and completed socio-demographic information and measures assessing child behaviour and emotional problems, and parenting style pre-, post-intervention, and at 12-month follow-up. **Results:** Although the children with ASD ( $n = 230$ ) had significantly higher rates of behaviour and emotional problems at all-time points compared to the children without ASD ( $n = 135$ ), both groups demonstrated significant decreases in behaviour and emotional problems post-treatment. These gains were maintained at 12-month follow-up for overall behaviour and emotional problems, disruptive behaviours, self-absorbed behaviours and communication disturbance. There was however a small increase in anxiety at 12-month follow-up for children without ASD only. Additionally, there was a continued decrease in social relating problems for the children with ASD, but not for those without ASD. A similar pattern of improvement and maintenance was found for parenting skills

(consistency, coercive and positive encouragement) between the parents of children with and without ASD. **Conclusion:** Overall, the community-based SSTP programme demonstrated a comparable effectiveness in reducing child behaviour and emotional problems and maintaining the gains during the 12-month follow-up period for children both with and without ASD.

**Keywords** ASD, behaviour and emotional problems, parenting skills, treatment

#### THE PREVALENCE AND PROFILE OF ANXIETY DISORDERS IN CORNELIA DE LANGE AND FRAGILE X SYNDROMES

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**Background:** Anxiety is common in neurodevelopmental disorders with particular syndromes at higher risk for specific types; however, little is known of how these meet diagnostic clinical criteria. This study investigated the prevalence and profile of anxiety disorders in individuals with Cornelia de Lange syndrome (CdLS) and fragile X syndrome (FXS). **Methods:** Caregivers of individuals with CdLS ( $n = 47$ ; 3–53 years) and FXS ( $n = 33$ ; 6–48 years) completed the Kiddie Schedule of Affective Disorders and Schizophrenia, alongside measures of ability (Vineland Adaptive Behaviour Scale) and autism spectrum disorder (ASD; Social Responsiveness Scale); across which groups were comparable ( $P > .05$ ). **Results:** No group differences were found in the number of individuals meeting *threshold* for at least one anxiety disorder (CdLS = 55.3%, FXS = 42.4%;  $P > .05$ ), but individuals with CdLS were significantly more likely to show comorbidity of disorders (CdLS = 23.4% FXS = 9.1%;  $P < .05$ ). The most common disorders in CdLS were specific phobias (48.9%), generalised anxiety disorder (21.3%) and selective mutism (16.7%), whereas in FXS, these were specific phobias (39.4%) and generalised anxiety disorder (12.1%). An additional 55.3% and 45.5% of individuals with CdLS and FXS scored *subthreshold* for anxiety disorders, with only 19.1% and 33.3%, respectively, scoring *not present* for any disorder. Associations between anxiety profiles and participant characteristics including age, ability and ASD characteristics will be described. **Conclusion:** Anxiety disorders were prevalent in CdLS and FXS. Interestingly, there were a number of individuals scoring only at *subthreshold* for anxiety disorders but still reporting significant impact on daily functioning. One difficulty was that many anxiety disorders require informants to report on internal thought processes, which is challenging for individuals with low cognitive ability and expressive language skills. This should be evaluated alongside the specific profiles of anxiety disorders and associated participant characteristics in these syndromes, in order to aid the understanding of underlying mechanisms and identification of opportunities for intervention.

**Keywords** anxiety disorders, Cornelia de Lange syndrome, fragile X syndrome, generalised anxiety disorder, intellectual disability, phobias

#### A CONTROLLED TRIAL OF SERTRALINE IN CHILDREN 2 TO 6 WITH ASD WITHOUT FRAGILE X SYNDROME

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**Background:** There is evidence of low serotonin production in the CNS of young children with autism spectrum disorder (ASD). Metabolomics studies demonstrate a depletion of the enzymes that metabolise tryptophan to serotonin in children with ASD. A 6-month controlled trial of low dose sertraline in children with fragile X syndrome (FXS) demonstrated efficacy on subtests of the Mullen (MSEL) vs. placebo. The current study follows a similar protocol in ASD. **Methods:** Fifty-eight children with ASD ages 24–72 months (mean 50 SD 11.66) were

enrolled in a 6-month double-blind controlled trial of low dose sertraline (2.5–5.0 mg/day). Primary outcome measures were the changes in MSEL expressive language raw score and combined age equivalent score. Additional measures included the CGI-I, VAS, ABC, SPMP, SRS2, PAS-R, VABSII and PLS5. Molecular biomarkers including the BDNF allelic variants were assessed. At enrolment, all children were receiving interventions from school/therapists for ASD. **Results:** Six patients discontinued the study due to adverse events (three hyperactivity, one increased aggression, one diarrhoea and one excessive screaming). Of 227 adverse events to date, all were mild or moderate except one serious adverse event (hospitalisation for viral URI complications) that was not related to study drug. Many children demonstrated a positive response to the study, including parent-reported effects on behaviour and language. Unblinding will occur in July 2018 when the last patient completes the trial. Analysis of the efficacy data will be presented at the SSBP conference. **Conclusion:** The response of children with ASD to low dose sertraline, including safety and overall efficacy, will be presented. Anticipated benefits will likely be in language and anxiety reduction. Molecular biomarkers may correlate with outcome.

**Keywords** ASD, treatment, sertraline

#### INTERVENTIONS FOR CHILDREN WITH AUTISM: IDENTIFYING WHAT WORKS FOR WHOM

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**Background:** Despite the heterogeneity of autism, most intervention research focuses on group outcomes; little is known about the individual characteristics of children who do, or do not, respond to treatment.

**Methods:** We explored factors predictive of treatment response, as opposed to variables related to prognosis in autism more generally, in two large-scale data sets: (1) 152 pre-school children involved in a parent-mediated, social-communication randomised control trial and (2) 240 school-aged children receiving social-cognition interventions. The Reliable Change Index was used to identify children as responders or non-responders to intervention. Logistic regression was used to identify baseline variables predictive of treatment response. **Results:** Group analyses indicated moderate-large improvements in each intervention group compared with treatment as usual (TAU). However, in both treatment and TAU conditions, some children failed to improve while others made considerable gains. None of the variables typically associated with a good prognosis in autism, such as cognitive, linguistic and social skills were predictive of treatment response. However, in the parent-mediated trial, TAU children in the site with greater social deprivation had a poorer outcome ( $P < .01$ ) than TAU children in other sites. In the social-cognition cohort, children with poorer baseline social skills were more likely to respond to intervention ( $P = .01$ ) than those with better-developed social skills. **Conclusion:** The findings illustrate the complexity and challenges of identifying factors related to individual responses to intervention; they also highlight the importance of distinguishing between prognostic indicators of natural improvement over time and variables that predict treatment outcome. To date, little is known about which children may benefit from a particular intervention or for whom it is contraindicated. Larger, multicentre trials are essential to understand the variables related to treatment response and to enable educators and clinicians to choose appropriately individualised interventions for children with autism.

**Keywords** autism, outcome, response to intervention

#### TOP 15 RESEARCH PRIORITIES IN TUBEROUS SCLEROSIS COMPLEX

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**Background:** Tuberous sclerosis complex (TSC) is an incurable genetic condition that affects approximately two million people worldwide. Patients' lives are impacted by the threat of tumour growth and by the burden of refractory epilepsy, disfiguring skin lesions or TSC-associated neuropsychiatric disorders (TAND). Quality of life, burden of illness and socio-economic impact of TSC are poorly researched. **Methods:** Inspired by methods established by the James Lind Alliance, the University of Amsterdam and the Fondation Motrice France, a priority-setting partnership in TSC was established and a multi-stakeholder dialogue for setting research priorities was conducted. Research questions were developed based on input from all stakeholders using focus groups, individual in-depth interviews and an online, Delphi-type information exchange, completed with data from literature. Priority setting was carried out using online voting in combination with facilitated deliberation workshops. **Results:** Focus groups and interviews with 24 patients and caregivers resulted in 350 uncertainties, which were translated into 62 researchable questions. These were submitted for refinement and prioritisation to a panel of representatives of six international patient organisations, resulting in 39 researchable questions and 8 urgent needs. In parallel, individual interviews of 19 healthcare practitioners and researchers resulted in a list of >250 uncertainties translated into 39 researchable questions, which were submitted for review and further input to 30 TSC experts. Integration of >200 comments and refinements led to 49 researchable questions which were then prioritised by online voting. The top 15 research priorities in TSC were agreed during a workshop that involved 10 patients and caregivers as well as 11 researchers and healthcare practitioners. **Conclusion:** These 15 priorities are intended to provide a platform for researchers, funding bodies and industry to ensure that future research funding and research activities focus on questions that are important to patients and families with TSC as well as their healthcare providers.

**Keywords** multi-stakeholder dialogue, research priority setting, stakeholder participation, tuberous sclerosis complex

#### FMR1 ALLELE SIZE DISTRIBUTION IN 35 000 MALES AND FEMALES: A COMPARISON OF DEVELOPMENTAL DELAY AND GENERAL POPULATION COHORTS

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**Background:** Developmental delay phenotypes have been associated with *FMR1* premutation (PM: 55–200 CGG repeats) and 'grey zone' (GZ: 45–54 CGG repeats) alleles. However, these associations have not been confirmed by larger studies to be useful in paediatric diagnostic or screening settings. **Methods:** This study determined the prevalence of

PM and GZ alleles in two independent cohorts of 19 076 paediatric referrals to developmental delay diagnostic testing through Victorian Clinical Genetics Service (cohort 1:  $N = 10\ 235$ ; cohort 2:  $N = 8841$ ), compared with two independent general population cohorts (newborn screening  $N = 1997$ ; carrier screening by the Victorian Clinical Genetics Service prepair programme  $N = 14\ 249$ ). **Results:** PM and GZ prevalence rates were not significantly increased ( $P > 0.05$ ) in either developmental delay cohort (male PM: 0.12–0.22%; female PM: 0.26–0.33%; male GZ: 0.68–0.69%; female GZ: 1.59–2.13%) compared with general population cohorts (male PM: 0.20%; female PM: 0.27–0.82%; male GZ: 0.79%; female GZ: 1.43–2.51%). Furthermore, CGG size distributions were comparable across data sets, with each having a modal value of 29 or 30 and  $\sim 1/3$  females and  $\sim 1/5$  males having at least one allele with  $\leq 26$  CGG repeats. **Conclusion:** These data do not support the causative link between PM and GZ expansions and developmental-delay phenotypes in paediatric settings.

**Keywords** developmental delay (DD), fragile X mental retardation 1 gene (*FMR1* gene), fragile X syndrome (FXS), premutation, prevalence

#### GENDER DIFFERENCES IN INTERNALISING PSYCHOPATHOLOGY AMONG YOUNG ADULTS ON THE AUTISM SPECTRUM

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**Background:** There is a growing body of literature regarding the impact of internalising psychopathology symptoms for adults on the autism spectrum. However, relatively little research has investigated whether the experience of anxiety or depression is different among males and females on the spectrum. The aim of this study was to explore any gender differences in internalising psychopathology among a sample of young adults on the spectrum. **Methods:** Participants comprised of 111 young adults (78 male, 33 female) on the spectrum aged 15–24 years from the baseline survey of the Longitudinal Study of Australian School Leavers with Autism (SASLA). Respondents completed the battery of questionnaires online. The measures examined in this analysis included Autism Quotient-Short (AQ-28), DSM-V Dimensional Generalised Anxiety Disorder Scale (GAD-D), Patient Health Questionnaire-9 (PHQ-9) and Emotion Regulation Questionnaire (ERQ). **Results:** An initial examination showed that despite no differences in overall Autism-Quotient scores, females had significantly higher levels of anxiety ( $F_{1,83} = 18.89, P < .001, \eta^2 = .14$ ) and depression ( $F_{1,81} = 8.16, P = .005, \eta^2 = .09$ ) compared to males on the spectrum. Further, it was found that a significantly higher proportion of females than males fell above the clinical cut-off on the GAD-D ( $P = .003$ ) and PHQ-9 ( $P = .031$ ). A hierarchical regression model was used to examine the relationship between emotion regulation and internalising psychopathology. It was found that among females, a higher emotion regulation ratio (i.e. greater use of emotional suppression relative to emotional appraisal) significantly predicted higher anxiety ( $\beta = .630, P = .009$ ) and depression symptoms ( $\beta = .912, P < .001$ ). No relationship was found for males on the spectrum. **Conclusion:** These results add to the literature suggesting that females on the spectrum experience significantly more internalising psychopathology difficulties than males. The findings also indicate a difference between the genders on the relationship between emotion regulation strategies and internalising psychopathology, which has important implications for intervention strategies.

**Keywords** autism spectrum disorder, autism spectrum disorder, psychopathology

#### SOCIAL IMPAIRMENT IN 22Q11.2 DELETION SYNDROME: A COMPARISON WITH IDIOPATHIC AUTISM SPECTRUM DISORDER

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**Background:** Behaviours characteristic of autism spectrum disorder (ASD) are common in 22q11.2 deletion syndrome (22q), and individuals with this deletion are diagnosed with ASD at higher rates compared with the general population. The current study sought to examine the causes of the social impairment seen in 22q by generating comparative perceptual, cognitive, linguistic, behavioural and emotional intermediate phenotype and comparing these with an age and IQ matched group of children with idiopathic ASD (iASD). It was expected that while superficially similar to iASD, social impairment in 22q would have a different aetiology, despite similar level of intellectual functioning and significant social challenges. **Methods:** Children aged 6–12 with either confirmed 22q [mean (SD) age: 9.3 (2.0); FSIQ: 84.0 (11.4)] or iASD [mean (SD) age: 9.6 (2.0); FSIQ: 84.1 (11.3)] were tested. Social Responsiveness Scale (SRS) and Social Communication Questionnaire (SCQ) screened participants for reciprocal social communication difficulties. Participants completed a clinician-blinded Autism Diagnostic Observation Schedule (ADOS Module 3) assessment with clinical best estimate (CBE). Measures of language (expressive/receptive, figurative and word generation), social cognition (theory of mind, emotion and gesture recognition) and executive functioning were collected. **Results:** Item-level comparison of ADOS ratings indicated areas of convergence and divergence between the groups. In the 22q group 47% (8/17) reported clinically significant ADOS scores. Clinically significant scores on all SRS, SCQ and ADOS measures were present for 23% (4/17) of individuals with 22q; however, only one participant also yielded a CBE diagnosis of ASD. Group differences on measures of social cognition (gesture recognition) were not reported ( $P > 0.05$ ). Divergence in language profile was observed via interaction effect for expressive/receptive language ( $P < 0.05$ ). **Conclusion:** We report evidence of divergent patterns in language abilities between 22q and iASD groups. Further, our findings suggest that parent reports such as the SRS may not be an effective predictor of the presence of ASD symptomatology in 22q.

**Keywords** 22q11.2, ASD, cognitive profile, cognitive profile, social cognition, social impairment, social phenotype

#### ARE LANGUAGE SCORES AN EARLY PREDICTOR OF CONVERSION TO PSYCHOSIS?

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**Background:** Patients with 22q11.2 Deletion Syndrome (22q11.2DS) have a 25% chance of developing schizophrenia (SZ), recently reported to follow cognitive decline. We also noted a decline in language scores from pre-school to school aged children and created a 'growth chart' of typical language development which we hypothesise may ultimately correlate with a predisposition to psychosis. **Methods:** We performed a retrospective chart review of 730 children, ages 4 months–21 years, with a laboratory confirmed 22q11.2 deletion, followed in the 22q and You Center at the Children's Hospital of Philadelphia and evaluated by a Speech-Language Pathologist using the Pre-School Language Scale (PLS)/the Clinical Evaluation of Language Fundamentals (CELF), stratified by test and age. A logarithmic model was used to determine line of best fit. **Results:** A significant decline in mean total test scores (MTTS) from pre-school to school age was observed. Specifically, the MTTS was 83.7 at 0 to <5 years, 71.25 at 5 to <10 years, 70.1 at 10 to <15 years and 66 at age 15 to <20 years. The steepest decline occurred between 0 to <5 years and 5 to <10 years, while differences in later groups revealed a much lower rate of change. Conversely, a group of children followed longitudinally displayed an increase in scores over time. **Conclusions:** We developed a novel 'language growth chart' for patients with 22q11.2DS and, despite a known association with significant delays in emergence of language, our data revealed the highest language scores in young children, followed by a striking rate of decline in the school-aged years and plateauing at approximately age 10 years. Notably, we also identified a sub-cohort of children with an increase in language scores over time. Thus, we plan to compare this data to existing records on patients with and without

cognitive decline and SZ, aiming to identify children with an increased risk for psychiatric disorders at an even earlier age.

**Keywords** 22q, chromosome, deletion, IQ, language, schizophrenia

### PARENTAL PSYCHOLOGICAL PROBLEMS AND PARENTAL STRESS IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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**Background:** Autism spectrum disorder (ASD) is defined by persistent deficits in reciprocal social interaction, communication and language, as well as stereotyped and repetitive behaviour. Children with ASD have higher rates of incontinence and gastrointestinal tract symptoms. Parents of children with ASD show more parental stress and psychological symptoms. The aim of the study was to examine stress and psychological symptoms in parents of children/adolescents with ASD with or without incontinence. **Methods:** Data of 51 children (43 boys, mean age = 9.7 years), consecutively presented in a tertiary outpatient clinic for autism, as well as 53 matched continent controls (43 boys, mean age = 10.2 years) were included in the study. All patients and their parents underwent the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R). All children received sonography (rectum, bladder), uroflowmetry, bladder diary, physical examination, IQ test, parental psychiatric interview and a questionnaire regarding incontinence and psychological symptoms (CBCL). Parents completed the Social Communication Questionnaire (SCQ), Adult Self Report (ASR) and a questionnaire on parental stress (ESF). **Results:** Thirty-seven children received a diagnosis of ASD in 14 patients ASD was excluded. Children with ASD had significantly higher CBCL-scores, more comorbid psychiatric disorders, as well as a significantly lower IQ. The ASD group had significantly higher rates of urinary incontinence (16.2%) than controls (0%). Parental stress and psychopathology was significantly higher in parents of children with autism. Parental stress can be significantly predicted by the total ASR score, parental role restriction and patient group but not by incontinence. **Conclusion:** Children with ASD have higher rates of urinary incontinence, as well as psychological problems. Parents of children with ASD experience more own psychological symptoms, which have a major influence on parental stress. Incontinence of their children does not increase parental stress, additionally.

**Keywords** Autism spectrum disorder, incontinence, parental stress, parental psychopathology

### COMMUNICATION IN ANGELMAN SYNDROME: AN ISOLATED PROBLEM OF SPEECH PRODUCTION?

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**Background:** Angelman syndrome (AS) is caused by deletion or alteration of gene UBE3A. Speech is absent for all genetic causes regardless of cognitive ability; however, it is not known if other forms of expressive communication are affected. By examining the communication profile of deletion and non-deletion genetic causes, we can ascertain whether (1) spoken language deficits dissociate from other communicative abilities and (2) if spoken language deficits are unrelated to general cognitive impairment. **Methods:** Questionnaire data were collected on receptive and expressive language and gesture use for children with AS (deletion ( $n = 18$ )  $M_{age} = 9.88$ ,  $SD = 4.58$ ; non-deletion ( $n = 22$ )  $M_{age} = 9.33$ ,  $SD = 3.50$ ). Gesture use (including intentionality) and verbal and non-verbal communication were also assessed using behavioural coding (deletion ( $n = 27$ )  $M_{age} = 9.75$   $SD = 3.83$ ; non-deletion ( $n = 10$ )  $M_{age} = 9.75$   $SD = 4.11$ ). **Results:** Non-deletion AS evidenced significantly better receptive ( $P < .001$ ) and expressive language ( $P = .001$ ) and more gesture use ( $P < .001$ ) than deletion AS, yet their expressive language was still impaired relative to TD children of similar receptive language abilities ( $P < .001$ ). There were minimal between group differences in amount of verbalisations ( $P = .025$ ) but non-deletion AS had a wider range of gestures, more intentional

communication and used significantly more symbolic forms of communication ( $P < .001$ ) than deletion AS. **Conclusion:** Spoken language skills dissociate from other communicative abilities in AS. While both groups were characterised by absent speech, gesture use and other non-verbal communication skills were present in both groups and were more evident in the non-deletion sample. Universal absence of speech in AS, even in individuals with relatively good non-verbal communication skills, implicates involvement of UBE3A in speech production. Evidence of intentional communication, despite absent speech, suggests that use of alternative communication aids would be effective in this population.

**Keywords** Angelman syndrome, communication, genotype-phenotype, gesture use, language, observational analysis

### CROSS-SYNDROME COMPARISON OF PSYCHOPATHOLOGICAL RISK FACTORS IN WILLIAMS SYNDROME, FRAGILE X SYNDROME AND PRADER-WILLI SYNDROME

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**Background:** Psychopathology is highly prevalent in adolescents and adults with several genetic syndromes associated with intellectual disability, including Williams syndrome (WS), fragile X syndrome (FXS) and Prader-Willi syndrome (PWS). However, little is known about associated risk factors. This study aims to identify whether age, health difficulties, adaptive ability and sensory processing impairments may predict or influence psychopathology in these groups. **Methods:** A questionnaire study was conducted with 111 parents/carers of individuals over the age of 12 (WS = 35, FXS = 50, PWS = 26; 74 were male). The mean age of the sample was 26.41,  $SD = 10.38$ . **Results:** Multiple regression analyses were utilised to examine predictors of psychopathology at group level. For the WS group, increased current health difficulties and sensory processing impairments predicted increased psychiatric disturbance  $F_{5,28} = 8.16$ ,  $P < .0001$ ,  $adj R^2 = .52$ . In PWS, only poorer adaptive ability was influential in predicting increased overall psychiatric disturbance ( $B = -1.41$ ,  $P = .001$ ), generalised anxiety ( $B = -0.37$ ,  $P = .006$ ) and hyperactivity ( $B = -0.38$ ,  $P = .003$ ). There were no significant predictors of psychopathology for individuals with FXS. **Conclusion:** This study highlights dissociations in the risk factors of psychopathology between the three syndromes. Adaptive ability may contribute to the development and maintenance of psychopathology in PWS, whereas health difficulties and sensory processing may be influential for individuals with WS. Identification of risk factors may be beneficial in assisting diagnosis and informing prevention strategies for psychiatric difficulties.

**Keywords** fragile X syndrome, Prader-Willi syndrome, psychopathology, risk factors, Williams syndrome

### BIOMARKERS FOR ALZHEIMER'S DISEASE IN DOWN SYNDROME

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**Background:** Older individuals with Down syndrome (trisomy 21) has a very high risk for developing dementia due to Alzheimer's disease, and accurate diagnosis is difficult in the context of premorbid intellectual impairments. A reliable biomarker for Alzheimer's disease-related decline would help to improve diagnosis and could also be used as surrogate markers in clinical trials of treatment to prevent decline. **Methods:** The Londowns consortium has established a large cohort of adults with Down syndrome ( $n > 450$  at baseline) who are being followed longitudinally with detailed assessments for cognitive decline and development of dementia symptoms, as well as blood samples for biomarker analysis. The presence of an additional chromosome 21 was confirmed genetically using saliva or blood samples; following DNA extraction, genome-wide single nucleotide polymorphism genotyping was performed using an Illumina OmniExpressExome array (San Diego, CA,

USA). We are using ultrasensitive single molecule array technology (SIMOA – Quanterix, Lexington, MA, USA) to measure plasma levels of biomarkers related to neurodegeneration (neurofilament light; NF-L), as well as A $\beta$ 42, A $\beta$ 40, tau [Human Neurology 3-Plex A assay (N3PA)], IL1b (Human IL-1 $\beta$  2.0), IL1 $\alpha$ , IL6 and TNFa (Human Cytokine 3-Plex A). **Results:** We will present biomarker data related to Alzheimer's disease (AD) in individuals with Down syndrome, compared to healthy controls and controls with early onset sporadic Alzheimer's disease. Most AD biomarkers in Down syndrome did not have a strong relationship with age except NF-L levels (Spearman's rho = 0.79,  $P < 0.001$ ), with a steep increase after age 40. NF-L were predictive of dementia status after adjusting for age, sex and APOE4. Baseline NF-L levels were also associated with longitudinal dementia status. **Conclusion:** NF-L is a biomarker for neurodegeneration in Down syndrome and has potential as surrogate marker in future clinical trials to prevent or delay dementia.

**Keywords** Alzheimer's disease, Down syndrome, fluid biomarkers, neurofilament light

#### GLOBAL METHYLOMIC PROFILING IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

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**Background:** Autism spectrum disorder (ASD) is an early onset, developmental disorder with a reported incidence of 1 in 68 people as stated by the Centers of Disease Control and Prevention. DNA methylation can play a role in the pathogenesis of ASD having a significant role in modulating gene expression. Indeed, it has been observed that genes that have a role in epigenetic pathways constitute a large percentage of the candidate risk genes for ASD. **Methods:** Samples from 44 age-matched participants (2–5 years old) including 23 subjects with ASD and 11 neurotypically developing (TD) children were investigated. DNA methylation was determined using the Illumina Human Methylation EPIC Bead Chip. ANOVA with FDR was used to identify differentially methylated CG sites between groups. Gene expression levels in a subset of genes were measured by qRT-PCR and compared between groups using ANOVA. **Results:** Using a  $P$ -value of .05, we found that 76 genes were significantly hypermethylated, and 694 genes were significantly hypomethylated in children with ASD compared to TD. When using more stringent criteria with a  $P$ -value less than .05

and fold change in methylation higher than 1.5, we found that children with ASD had a total of 47 genes that were differentially methylated compared to TD including znf587, NF2 and the C11orf31 genes. Out of the 47 genes, 30 were hypermethylated and 17 hypomethylated. qRT-PCR experiments showed that the differential expression of a subset of genes was in line with their methylation status in all three groups. **Conclusion:** This study shows a potential role for altered DNA methylation in the pathology of ASD and may help in the diagnostic classification of children with ASD based on epigenetic markers. In addition, it may pave the way for developing therapeutic interventions that could reverse the altered methylomic profile in children with neurodevelopmental disorders.

**Keywords** ASD, epigenetics, expression, methylation

#### EMOTIONAL DYSREGULATION, LOW MOOD AND ANXIETY IN RUBINSTEIN-TAYBI SYNDROME

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**Background:** Individuals with Rubinstein-Taybi syndrome (RTS) are reported to experience anxiety and mood disorders in adolescence and adulthood. There is increasing evidence that in the general population emotional dysregulation may be a risk marker for the emergence of these difficulties. The aim of this study was to examine the associations between low mood, anxiety and emotional dysregulation in RTS at two time points (2010 and 2018). **Methods:** Parents/carers ( $N = 48$ ) of children and adults with RTS (mean age: 21.54; range: 6–53 years) completed the Mood, Interest and Pleasure Questionnaire (MIPQ) and the Behaviour Rating Inventory of Executive Function (BRIEF-P) in 2010 as part of a large-scale cross-syndrome study. In 2018, these measures were repeated along with the Anxiety and Depression and Mood Scale. **Results:** In the cross-sectional analysis, low mood as measured by the MIPQ, was associated with poorer inhibitory control ( $R = -.43$ ,  $P = .002$ ) and poorer emotional regulation ( $R = -.42$ ,  $P = .002$ ) on the BRIEF-P. Low mood was not associated with ability level. These findings will be discussed along with preliminary findings from the longitudinal study. **Conclusion:** The findings provide further support for a link between emotional dysregulation and mental health difficulties and suggest that emotional dysregulation should be explored further in RTS. Observational and psychophysiological measures of emotional dysregulation in RTS should be pursued to validate these findings.

**Keywords** anxiety, emotional dysregulation, mood, Rubinstein-Taybi syndrome