MDHS Graduate Research Conference 2020

Paediatrics Booklet

https://mdhs.unimelb.edu.au/mdhs-graduate-research-conference-2020

mdhs-grconference@unimelb.edu.au

MESSAGE FROM THE CHAIRS

Dear Delegates,

Welcome to the virtual inaugural Medicine, Dentistry and Health Science Graduate Research Conference 2020 (MDHS GR Conference), a student conference for all biomedical graduate research students that are part of the MDHS Faculty of the University of Melbourne. The organising committee is made up of members from 11 different student society across the MDHS faculty campus. The conference schedule consists out of 12 parallel session covering a variety of interesting topics and accommodating our student talks as well as national and international keynote speakers, Science Communication workshop and a Career Panel Discussion. This event was only possible due to the generous support of the University of Melbourne and the Graduate Student Association (GSA).

We hope that MDHS GR Conference will provide you with opportunities to listen to national and international leaders talking about their ground-breaking research in different biomedical fields and communicate your research to a broad scientific audience. Despite the fact that this conference will be virtually it will give you a unique chance to meet and network with peers from different research fields engage in discussions. We hope that the MDHS GR Conference will inspire you with new possibilities for your future career by listening to our invited speakers from academia and industry.

We wish you all the best for your presentation and hope you enjoy the event and get novel project ideas, career opportunities and new connections out of it.

Martha Blank & Alexander Anderson

(Chair & Deputy-Chair of the Medicine, Dentistry and Health Science Graduate Research Conference 2020)

GENERAL PROGRAM

08.00 - 08.15 Conference Opening & Welcoming Address
Professor Alex Boussioutas and Martha Blank

08.15 - 10.00 Session 1

10.00 - 10.30 Break

10.30 - 12.30 Session 2

12.30 - 13.00 Break
Virtual Socialise

13.00 - 14.30 Science Communication Workshop
Dr. Shane Huntington

14.30 - 16.00 Break
Virtual Socialise | Networking | Games

16.00 - 17.00 Careers Panel Discussion
A/Prof. Nicholas Opie | Dr. Danijela Mirosa | Dr. Ashish Sethi
Dr. Maryam Hussain | Dr. Simranpreet Kaur

17.00 - 19.00 Session 3

19.00 - 20.00 Award Ceremony & Conference Closing
Martha Blank and Alexander Anderson

SCIENCE COMMUNICATION WORKSHOP

Dr. Shane Huntington

Dr. Shane Huntington has been providing consulting services in communication and strategy for over 20 years. As a successful broadcaster, business owner, academic and strategist he draws together experience from multiple sectors, offering clients a more detailed and analytical approach than competitors. Shane has trained thousands of people to communicate more effectively, especially in fields of research. His unique and engaging style has led to him delivering programs to some of Australia's most prestigious institutions.

CAREERS PANEL DISCUSSION

A/Professor Nicholas Opie

Synchron Founding Director and CTO
Co-Lab Head of the Vascular Bionics Laboratory, The University of Melbourne

Dr. Danijela Mirosa

Franchise Director of Oncology for the Oceanic Cluster
Takeda Pharmaceuticals

Dr. Ashish Sethi

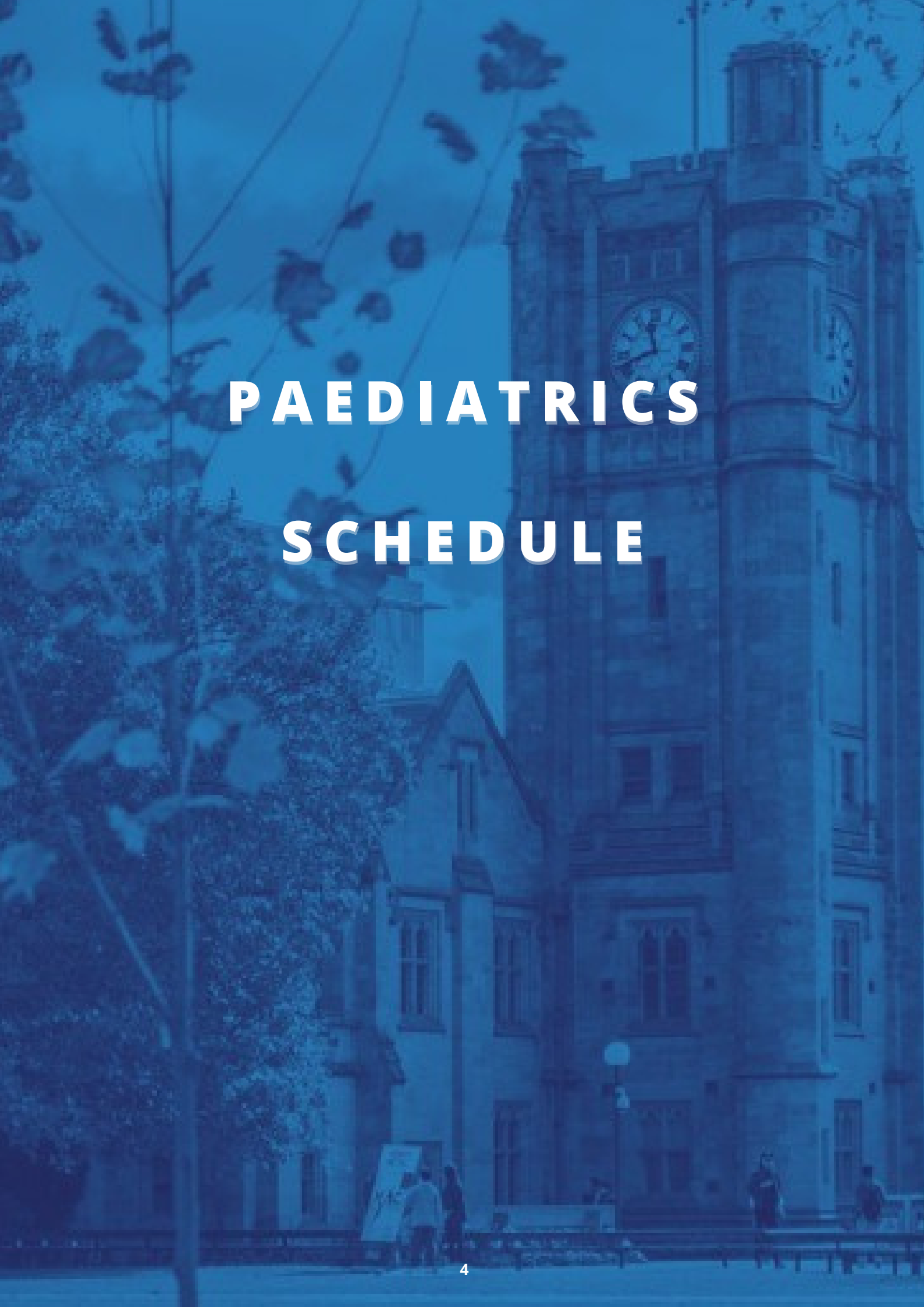
Postdoctoral Research Fellow
Department of Biochemistry & Molecular Biology, TheUniversity of Melbourne

Dr. Maryam Hussain

Medical Science Liaison
Boehringer Ingelheim

Dr. Simranpreet Kaur

Postdoctoral Researcher
MitoBrain Murdoch Children's Research Institute



PAEDIATRICS SCHEDULE

PAEDIATRICS

SCHEDULE

SESSION 1

SESSION 2

SESSION 3

PAEDIATRICS

Keynote Speakers

A/Professor Matthew Greenhawt
Children's Hospital Colorado
University of Colorado
School of Medicine

Session 1 09.30- 10.00 am

A/Prof. Matthew Greenhawt earned his medical degree from Tufts University School of Medicine, Boston, Massachusetts; completed a pediatrics residency at Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia Presbyterian Medical Center, New York, New York, and an allergy/immunology fellowship at the University of Michigan in Ann Arbor, Michigan. He also holds an MBA from Tufts University and a master's of science degree in health and healthcare policy from the University of Michigan, Rackham School of Graduate Studies. Dr. Greenhawt is an Associate Professor with the Department of Pediatrics, Section of Allergy and Immunology at Children's Hospital Colorado and the University of Colorado School of Medicine, and is the director for the Children's Hospital Colorado Food Challenge and Research Unit.

Dr. Greenhawt is board certified in Pediatrics and Allergy/Immunology. He is a member of the American Academy of Allergy, Asthma & Immunology, American Academy of paediatrics, American College of Allergy, Asthma & Immunology, and European Academy of Allergy and Clinical Immunology. He is an associate editor for the Annals of Allergy, Asthma and Immunology, and a member of the Joint Taskforce of Allergy Practice Parameters. Dr. Greenhawt's research interests include, shared decision making, food allergy cost-effectiveness and comparative effectiveness research, food-allergic diseases health services research, primary/secondary prevention and treatment of food allergy, and food allergy public policy. He has authored a number of peer-reviewed articles, abstracts, and book chapters. He is the immediate past chair of the ACAAI Food Allergy Committee, and is a member of multiple AAAAI, ACAAI, and EAACI committees.

Determining Levers of Cost-effectiveness for Screening Infants at High Risk for Peanut Sensitization Before Early Peanut Introduction.
Greenhawt M, Shaker M.JAMA Netw Open. 2019 Dec 2;2(12):e1918041. doi: 10.1001/jamanetworkopen.2019.18041. PMID: 31860109; PMCID: PMC6991237.

Professor Julie Bines
Murdoch Children's Research Institute
Royal Children's Hospital
University of Melbourne

Session 2 10.30 - 11.00 am

Julie Bines is the Victor and Loti Smorgon Professor of Paediatrics at the University of Melbourne and Head of Clinical Nutrition at the Royal Children's Hospital. She leads the Enteric Disease Group at Murdoch Children's Research Institute working to develop an affordable novel rotavirus vaccine, RV3-BB vaccine, aimed at preventing rotavirus disease from birth in infants worldwide. She has led clinical trial of this vaccine in Australia, New Zealand, Indonesia and Malawi. Professor Bines is Director of the WHO Collaborative Centre for Child Health and the WHO Rotavirus Regional Reference Laboratory for the Western Pacific Region. She has served as a consultant for WHO in a number of roles including on the Steering Committee for Enteric Disease Vaccines and the development of the roadmap for assessment of Vaccines against Antimicrobial resistance and developed the generic protocol for vaccine safety surveillance for rotavirus vaccines and the Brighton Collaboration clinical case definition for intussusception.

Human Neonatal Rotavirus Vaccine (RV3-BB) to target rotavirus from birth.
Bines JE, AT Thobari J, Satris CD, Handley A, Watts E, Cowley D, Newati HN, Ackland J, Standish J, Justice F, Icanervilla AJ, Byars G, Lee KJ, Bachtair NS, Barnes GL, Bishop RF, Kirkwood CD, Buttery JC, Soenarto YD. *New England Journal of Medicine* 2018: 378:719-30.

PAEDIATRICS

Keynote Speakers

Dr. Erich Rutz
Murdoch's Children's Research Institute
Royal Children's Hospital
Danube University Krems
Univeristy of Basel
The University of Melbourne

Session 2 12.00 - 12.30 pm

Dr. Erich Rutz has recently joined the orthopaedic department and The Hugh Williamson Gait Laboratory at the Royal Children's Hospital (RCH). For the last 15 years he worked as a consultant at the University Children's Hospital Basel, Switzerland, where he was Head of the Gait Laboratory and Head of Neuromuscular Hip Surgery Programme. He has a strong interest in all neuromuscular conditions and in particular in cerebral palsy (CP). 10 years ago, he worked as a research fellow in the Hugh Williamson Gait Laboratory at RCH on a major project "Outcomes of Single-event Multilevel Surgery (SEMLS)" in children with CP. Erich focuses on the surgical treatment of disabled, ambulant and non-ambulant, children. His surgical expertise is in both surgery for ambulant children (SEMLS) and one-stage, hip reconstruction. Dr Rutz has experience in and enjoys the challenges of all areas of paediatric orthopaedics and trauma surgery. He has written more than 60 scientific papers and 17 book chapters and completed his habilitation thesis ("Venia Docendi") in 2013 at the medical faculty of the University Basel, which is the highest university degree that can be awarded for orthopaedics and traumatology of the musculoskeletal
system. In addition the completion of his PhD thesis in biomechanics is intended by end of 2020. Dr. Rutz' academic work has been recognised by eight national and international awards. In his leisure time he enjoys spending time with his family, playing the violoncello, and (pre COVID-19) travelling for teaching and holiday.

Stability of the Gross Motor Function Classification System after single-event multilevel surgery in children with cerebral palsy
Erich Rutz, Oren Tirosh, Pam Thomason, Alexej Barg, H Kerr Graham. *Dev Med Child Neurol* 2012 Dec;54(12):1109-13.

ABSTRACTS

PAEDIATRICS

Infant pacifier sanitization and risk of food allergy

Victoria X. Soriano[1,2], Jennifer J. Koplin[1,2], Mike Forrester[3,4,5], Rachel L. Peters[1,2], Martin O'Hely[3,8], Shyamali C. Dharmage[6], Rosemary Wright[7], Sarath Ranganathan[2,8], David Burgner[2,8], Kristie Thompson[10], Terence Dwyer[11,12], Peter Vuillerman[3,4,8] & Anne-Louise Ponsonby[6,8,13]

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2 Department of Paediatrics, University of Melbourne, Parkville, Australia
3 School of Medicine, Deakin University, Geelong, Australia
4 Children's Services, Barwon Health, Geelong, Australia
5 St John of God Hospital, Geelong, Australia
6 Allergy and Lung Health Unit, School of Population and Global Health, University of Melbourne, Parkville, Australia
7 National Centre for Epidemiology and Population Health, Research School of Population Health, Australian National University, Canberra, Australia
8 Murdoch Children's Research Institute, Parkville, Australia
9 Child Health Research Unit, Barwon Health, Geelong, Australia
10 Queensland Alliance for Environmental Health Sciences, The University of Queensland, Queensland, Australia
11 Heart Research Group, Murdoch Children's Research Institute, Parkville, Australia
12 Nuffield Department of Women's & Reproductive Health, University of Oxford, Oxford, United Kingdom
13 Neuroepidemiology Research Group

Introduction: Environmental microbial exposure plays a role in immune system development and susceptibility to food allergy. Our objective was to investigate if infant pacifier use, with further consideration of sanitization, in early life changes food allergy risk at age 1.

Methods: The birth cohort recruited pregnant mothers at less than 28 weeks gestation in southeast Australia with 894 families followed up when infants turned 1 year. Infants were excluded if born under 32 weeks, with a serious illness, major congenital malformation, or genetic disease. Questionnaire data were collected at recruitment and infant ages 1, 6, and 12 months. We examined pacifier use and pacifier sanitization (defined as the joint exposure of a pacifier and cleaning method). Challenge-proven food allergy was measured at age 1 year. Multivariable logistic regression models were used to assess associations, adjusted for known food allergy risk factors.

Results: Any pacifier use at 6 months was associated with food allergy at 1 year (aOR, 1.94; 95% CI, 1.04-3.61), but not pacifier use at other ages. This overall association was driven by the joint exposure of pacifier-antiseptic use (aOR, 5.88; 95% CI, 2.17-15.94) compared to no pacifier use. Among pacifier users, antiseptic cleaning was still associated with food allergy (aOR, 3.88; 95% CI, 1.55-9.72), compared to no antiseptic use. Further, increased use of antiseptic cleaning at 0, 1, or 2 interviews over the first 6 months was associated with higher food allergy risk (p trend=0.029). Using no antiseptic at 6 months was not associated with food allergy.

Conclusion: This is the first report of pacifier-antiseptic combination being positively associated with food allergy. Future work should investigate underlying biological processes, including the impact of oral microbiome on immune regulation in the first year of life.

PAEDIATRICS

Single cell RNA analysis of hematopoietic cells derived from human induced pluripotent stem cells reveals similar transcriptional gene expression to putative hematopoietic stem cells isolated from human AGM

Jacky Li[1,2], Elizabeth S Ng[1], Edouard G Stanley[1,2,3] & Andrew G Elefanty[1,2,3]

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[2] Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Victoria 3052, Australia
[3] Department of Anatomy and Developmental Biology, Monash University, Clayton, Victoria 3800, Australia

Introduction: Hematopoietic stem cells (HSC) that support life long blood formation in humans first emerge during embryogenesis from the ventral floor of the aorta after day 32 of gestation. Clusters of blood cells emerge from the aortic floor via endothelial to hematopoietic transition (EHT) and rare preHSCs and HSCs from this population then migrate to colonize the fetal liver and later the bone marrow. Cells similar to these preHSCs and HSCs can be generated in vitro from differentiated human pluripotent stem cells (hPSCs). This thesis interrogates the transcriptional profiles of in vitro generated hematopoieic cells to determine their similarity to preHSCs and HSCs isolated from early human aorta.

Methods: Human PSCSs were differentiated to preHSC and HSC-like cells under different combination of mesoderm induction factors in an embryoid body based protocol for 14 days. Hematopoietic cells from each culture were isolated and single cell RNA sequencing was performed using the 10X Genomics platform and Illumina sequencing. Bioinformatics analysis used the Seurat package of the R suite. Aliquots of cells from each sample were also transplanted into immunodeficient mice to determine their repopulating capacity.

Results: Bioinformatic analysis focused on one sample that was differentiated under conditions that yielded superior engraftment of immunodeficient mice. There were 17 distinct cell lineage clusters including one arterial like endothelial cell cluster (AEC), three hematopoietic stem cell-like clusters (SC1, SC2 and SC3) as well as myeloid, erythroid and monocyte progenitor clusters. Co-expression of key arterial gene markers with stem cells associated genes in the SC3 cluster suggested that these cells differentiated from the cells in the AEC cluster. This mirrored the expression patterns of cells isolated from primary human embryo samples. Cells from the SC3 cluster were closely aligned to the other two stem cell-like clusters SC1 and SC2. Cells from SC1 appeared to mark precursors of erythroid, megakaryocyte clusters and eosinophil granulocyte type cells, whilst SC2 cells appeared to differentiate towards dendritic cell and monocyte cell clusters.

Conclusion: Comparing the transcriptional profiles of in vitro differentiated hPSCs with cells isolated from Carnegie stage 13 to 15 human aortic blood cells, revealed that the expression of key HSC and lineage associated genes was mirrored in hPSC derived HSCs. These transcriptional similarities between in vitro HSC-like cells and primary human embryonic HSCs bodes well for the potential generation of patient-specific HSCs derived from hPSCs that may be used in regenerative therapies

PAEDIATRICS

Genetic diagnostic outcomes in a cohort of individuals with cortical malformations

Matthew Coleman[1,2], George McGillivray[2,3], Susan M White[2,3], Lyndon Gallacher[2,3], Sarah EM Stephenson[1,2], Rick J Leventer[1,2,4] & Paul J Lockhart[1,2]

1 Bruce Lefroy Centre for Genetic Health Research, Murdoch Children's Research Institute, Victoria, Australia
2 Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia
3 Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Victoria, Australia
4 Department of Neurology, Royal Children's Hospital, Melbourne, Victoria, Australia

Introduction: Malformations of cortical development (MCDs) encompass a wide spectrum of conditions that result from abnormal brain development, including polymicrogyria, periventricular nodular heterotopia and focal cortical dysplasia. MCDs affect ~1 in 2,500 children and can result in epilepsy, developmental delay and cerebral palsy. Although multiple molecular pathways have been identified, ~40% of MCD cases still lack a genetic diagnosis after standard clinical diagnostic testing.

Methods: This study aimed to determine the genetic diagnostic yield in a small, cross-sectional cohort of MCD patients using clinical whole exome sequencing (WES) and trio design. Nine paediatric MCD cases of unknown aetiology were recruited to the Royal Children's Hospital Undiagnosed Disease Program or Accelerated Gene Identification Program. These cases were unsolved following standard clinical testing. Genomic DNA from the proband and parents was analysed by WES in collaboration with the Broad Center for Mendelian Genomics. WES data was analysed using SeqR, an open source variant curation software, and findings were separated into high confidence variants and low confidence variants. High-confidence candidate variants, predicted damaging by in silico methods, were identified in sequence data and classified as pathogenic, likely pathogenic or variants of unknown significance according to the American College of Medical Genetics and Genomics guidelines.

Results: Putative pathogenic variants were identified in 3/9 cases (33.3%). Novel single nucleotide variants were identified in ZIC2 (c.*57G>A), COL4A1 (p.G212S) and PLAG26 (p.Y790*; p.A633V), all genes previously associated with MCD. Variants of unknown significance (VUS) were identified in a further 2/9 cases (22.2%), in DYNC1H1 (p.V1821A) and MACF1 (c.*297A>C) genes.

Conclusion: Genetic diagnoses assist prognosis, genetic counselling and precision medicine. The diagnostic rate of 33.3% achieved in this study is consistent with previous studies of clinically unsolved MCD cases. These findings highlight the highly heterogeneous nature of MCDs and the value of a trio WES approach as an effective method for genetic diagnosis in clinically unsolved cases of a phenotypically diverse and heterogeneous disorder. This study was limited by the depth of the WES (~100x), which made it difficult to detect low level mosaic variants, and the coverage of WES, which often does not capture non-coding variants, repeat expansions or intronic variants. Whole genome sequencing or deep sequencing of target tissues, such as brain tissue, may assist to increase the diagnostic yield in the unsolved cases of this cohort. Additional functional analysis would be useful to interpret candidate VUS.

PAEDIATRICS

Is Sharing Caring? – Exploring the Experiences of Registered Nurses with disclosing medical information to children

Mandy El Ali[1,4], Lynn Gillam[1,2], Clare Delaney[1,2] & Sharon Licqurish [3]

1 The University of Melbourne, Faculty of Medicine, Dentistry, and Health Sciences, Melbourne Victoria, Australia.
2 The Royal Children's Hospital Children's Bioethics Centre, Parkville, Victoria, Australia.
3 Monash University, Faculty of Medicine, Nursing and Health Sciences, Chancellors Walk, Wellington Road, Clayton, Victoria, Australia.
4 The Australian Catholic University, Faculty of Health Sciences, 8-14 Brunswick street, Fitzroy, Victoria, Australia.

Introduction: Sharing of medical information with children in hospital is encouraged in theory, but variable in practice, particularly for younger children who can be seen as not able to understand or process information. Parents sometimes tell hospital staff to withhold information from children. The nurse's experience in caring for children with serious illness where a directive of non-disclosure is given has been largely ignored. We aim to explore the experience of nurses in sharing information with children and their families in general, and in the particular situations where they have been asked not to share information.

Methods: This is a qualitative study using Colaizzi's phenomenological methodology. We are recruiting Australian nurses who have cared for hospitalised seriously ill children in the last five years and interviewing them about their experiences. Recruitment has been through distribution of a flyer, through professional organisations, online platforms and snowballing. Due to COVID-19, interviews have been undertaken remotely through Zoom or Microsoft Teams platforms. The interviews are semi-structured and have been transcribed verbatim. The transcribed interview data is currently being analysed thematically.

Results: Seventeen nurses have participated, and preliminary analysis has suggested that nurses negotiate the relationships with children and their families and their professional responsibilities as a team member by practicing within what they perceive is their scope of practice. Participants have also expressed that the rapport they build with the children and their families, puts them in a position of trust, and they feel that there is an underlying moral obligation of advocacy to ensure the child understands their diagnosis, treatment and prognosis.

Conclusion: Early results suggest that nurses finding it difficult to fulfill what they see as their professional obligations when information is not being shared with children. This is complicated by nurses' position in health care hierarchy and a sense of lack of professional autonomy in relation to what they perceive as a limit in the amount or type of information they can give children and families. Data collection and analysis is continuing and will guide and inform future recommendations that supports the child's and family's health and well-being.

PAEDIATRICS

Impact of Rapid Exome Sequencing of Critically Ill Newborns on the Parent-Child Relationship

Bowman-Smart, Hilary[1,2], Vears, Danya[1,3], Stark, Zornitza[1,2,4,5]& Gyngell, Christopher[1,2]

1 Murdoch Children's Research Institute, Parkville, Victoria, Australia
2 Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia
3 Melbourne Law School, University of Melbourne, Parkville, Victoria, Australia
4 Victorian Clinical Genetics Services, Parkville, Victoria, Australia
5 Australian Genomics Health Alliance, Parkville, Victoria, Australia

Rapid exome sequencing (rES) of critically ill infants provides diagnoses much more quickly than traditional genetic testing, impacting treatment decisions and clinical management. Yet rES raises complex ethical issues, such as how a diagnosis in such early stages of life can impact the parent-child relationship.

Between 2018 and 2019, 108 critically ill infants underwent rES as part of a multisite Australian feasibility study, with 51% receiving a diagnosis. We explored the attitudes and experiences of 61 parents involved in the study using a mixed methods survey. Quantitative data was analysed using the t-test and Fisher's exact test. Qualitative data was analysed using content analysis.Receiving a diagnosis or a possible associated variant was correlated with parents having altered thinking about their child (p=0.018). Using the PedsQL 2.0 Family Impact Module, we found that the sample had a mean family functioning score of 50.4 out of 100. Parents expressed that having testing for their child had several benefits, such as allowing them to feel informed, accept the diagnosis, and prepare for challenges ahead. Parents mentioned that the information helped them make decisions about the most appropriate care for their child. However, parents also reported grief and fear for their child's future, with some finding the result difficult to accept.As the potential for implementing rES for infants in the Australian healthcare system increases, these results can help inform how genetic health professionals can best support parents and families, both when the test is offered and after result delivery.

PAEDIATRICS

Impacts of Covid 19 on anorexia nervosa and atypical anorexia nervosa prevalence and severity in a tertiary eating disorders service

Gabriella Springall[1,2], Michael Cheung[1,2,3] & Michele Yeo[3]

1 The University of Melbourne, Melbourne, VIC, Australia
2 Murdoch Children's Research Institute, Melbourne, VIC, Australia
3 Royal Children's Hospital, Melbourne, VIC, Australia

Introduction: The impact of the coronavirus (COVID-19) pandemic on mental health and eating disorders is becoming increasingly evident. Existing research reveals elevated levels of anxiety, depression, and stress alongside increased restricting, binging, purging and exercise behaviours. However, reasons for declining mental health and the onset of eating disorder behaviours, as well as how the treatment of individuals with these conditions is affected, remains unclear. This study aimed to identify underlying causes of eating disorder onset amidst the COVID-19 pandemic in Australia; with a particular focus on anorexia nervosa and atypical anorexia nervosa.

Methods: A four-year retrospective chart review of all patients presenting to The Royal Children's Hospital Eating Disorder Service in Melbourne between January and September was undertaken. The incidence of each eating disorder diagnosis, in addition to physical and psychological markers of condition severity, were extracted from the database and patient medical records. A total of 342 patients were reviewed and data was compared between years via single-factor analyses of variance. Comments from clinicians, patients, and their families, relating to the impact of COVID-19 were also noted.

Results: Anorexia nervosa and atypical anorexia nervosa diagnoses accounted for the largest proportion of patients each year and have increased in presentation over this time period. COVID-19 lock-down, resulting in isolation and loneliness, lack of normal routine and motivation, minimal distraction from anorexic thoughts, and the cessation of community sport was recognised as the trigger for 41.5% of patients eating disorder behaviours in 2020. A further 13.5% of patients recorded a relapse in recovery during COVID-19 lock-down. There was no significant difference in condition severity across years ($p > 0.05$) despite increased cases and reported relapses. Lastly, there was a split preference for telehealth and online learning versus face-to-face. Greater flexibility offered by telecommunication had the potential to aid treatment; although an overall lack of engagement was also recognised.

Conclusion: Outcomes of this study provide insight into the underlying cause of eating disorder development during a pandemic; highlighting the need for increased support during this time. In particular, greater monitoring of restrictive eating and exercising behaviours may be required. Assessment of telehealth and online learning suitability is integral to patient recovery. Treatments tailored to individual circumstances will improve uptake and engagement. Additional research is required to establish an evidence base to further diminish adverse consequences of the current, and future, crises.

PAEDIATRICS

Preventing Extubation Failure in Extremely Preterm Infants With Non-Invasive Respiratory Support

Anna Kidman [1,2,3], Brett Manley [1,2], Rosemarie Boland [1], Peter Davis [1,2] & Risha Bhatia [3]

1 Department of Obstetrics and Gynaecology, The University of Melbourne, Australia
2 Newborn Research Centre, The Royal Women's Hospital, Melbourne, Australia
3 Monash Newborn, Monash Children's Hospital, Melbourne, Australia

Background: Extremely preterm infants born <28 weeks' gestation often require invasive mechanical ventilation. To avoid bronchopulmonary dysplasia and other morbidities, clinicians aim to extubate to non-invasive respiratory support as soon as possible. However, extubation failure occurs in up to 60% of extremely preterm infants. Our aim was to compare non-invasive respiratory support modes used post-extubation in extremely preterm infants.

Methods: A systematic review performed according to PRISMA guidelines using Cochrane Neonatal Review Group methods. Data were pooled and analysed using Review Manager v5.

Results: Five modes of non-invasive respiratory support were identified, with three included in the review: nasal continuous positive airway pressure (nCPAP), nasal intermittent positive pressure ventilation (NIPPV, both synchronized and non-synchronized with the infant's breathing) and nasal high flow (nHF). Fifteen studies with 1926 infants were included in the quantitative synthesis. Synchronised NIPPV was more effective in preventing extubation failure than nCPAP RR 0.29 [95% CI 0.10, 0.86], NNT 2 infants. Fixed pressure ventilator derived NIPPV compared with nCPAP reduced extubation failure: RR 0.47 [95% CI 0.23, 0.97], NNT 3. Higher nCPAP pressures (≥ 8cm H2O) vs. lower pressures reduced extubation failure RR 0.59 [95% CI 0.43, 0.81], NNT 5. Nasal high flow was not inferior to nCPAP in reducing extubation failure in EP infants.

Conclusions: NIPPV when synchronised and ventilator derived may be superior than nCPAP when extubating extremely preterm infants. Promising new modes of respiratory support (nHFOV and NI-NAVA) require further evaluation before widespread use.

PAEDIATRICS

High resolution impedance manometry in children with oesophageal atresia

Sharman Tan Tanny[1,2,3], Assia Comella[1,2,4], Lisa McCall[5], John Hutson[1,2,3], Mark Safe[1], Warwick Teague[1,2,3], Taher Omari[5] & Sebastian King[1,2,3]

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[2] Murdoch Children's Research Institute, Melbourne, VIC, Australia
[3] The University of Melbourne, Melbourne, VIC, Australia
[4] Monash University, Melbourne, VIC, Australia
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Introduction: Oesophageal atresia (OA) +/- tracheo-oesophageal fistula (TOF) is the most significant congenital oesophageal anomaly, affecting 1 in 2600 newborns. Despite successful surgery, up to 85% of survivors have dysmotility into adulthood, leading to poor food bolus transport, choking, and even death. Currently, there is no reliable way to predict which patients will develop significant dysmotility. Using high resolution impedance manometry (HRIM), this study aimed to identify oesophageal motility patterns in OA +/- TOF patients.

Methods: Utilising a prospective longitudinal cohort study design, this study focused upon patients < 18 years. Utilising HRIM, motility patterns in OA +/- TOF patients were studied. Repeat assessments were performed, in a selected group of patients, at six-monthly intervals.

Results: 66 patients (M:F = 40:26, median age 14.8 months [3.8 months – 17.4 years]) completed 115 HRIM studies. The majority (56/66, 84.8%) of patients had OA with a distal TOF (the most common subtype). An associated anomaly was seen in 22/66 (33%) patients, oesophageal dilatation was performed in 38/66 (58%) patients, and fundoplication was performed in 8/66 (12%) patients. 29/66 (43.9%) patients underwent one study, 26/66 (39.4%) patients underwent two studies, 10/66 (15.2%) patients underwent three studies, and 1/66 (1.5%) patients underwent four studies.

Three common motility patterns were demonstrated: (1) aperistalsis (23/66, 34.8%); (2) distal oesophageal contraction (22/66, 33.3%); and; (3) pressurisation (6/66, 9.1%). A minority demonstrated combination patterns, including aperistalsis with weak distal contraction (7/66, 10.6%), and aperistalsis with pressurisation (2/66, 3.0%). Normal motility patterns were seen in 3/66 (4.5%), and only in patients with an isolated TOF (with oesophageal continuity from birth). At repeat assessment, 17/25 (68.0%) of those with two analysable studies maintained their initial motility patterns, while 6/9 (66.7%) of those with three analysable studies maintained their initial motility patterns.

Conclusion: The application of high resolution impedance manometry in patients with oesophageal atresia +/- tracheo-oesophageal fistula allows for objective identification of distinct and reproducible motility patterns. This novel technique allows for risk-stratification of patients, facilitating closer follow-up of those at high risk of morbidity.

PAEDIATRICS

Improving neonatal intubation safety: apnoeic oxygenation time in preterm infants

Hodgson K[1,2,3], Kothari R[1], Manley B[1,2,4], Davis P[1,2,4], Thio M[1,2 ,3,4] & O'Currain E[5]

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2 Department of Obstetrics and Gynaecology, The University of Melbourne, Melbourne, Victoria, Australia
3 Paediatric Infant Perinatal Emergency Retrieval, Royal Children's Hospital, Melbourne, Victoria, Australia
4 Murdoch Children's Research Institute, Melbourne, Victoria, Australia
5 University College Dublin, Dublin, Ireland

Introduction: Neonatal endotracheal intubation is an essential, but potentially destabilising procedure. Rates of successful intubation at the first attempt are relatively low, and rates of physiological instability are high, when compared with intubations in paediatric and adult populations. The Neonatal Resuscitation Program recommends a time-based limit (30 seconds) for intubation attempts, but there are limited physiological data to support this recommendation. Apnoeic oxygenation time (AOT) is the time until a specified peripheral oxygen saturation is reached during apnoea and may be useful as a marker of physiological instability. To date, AOT has not been reported in preterm infants. The aim of this study was to describe the AOT of preterm infants undergoing elective endotracheal intubation, in order to inform recommendations regarding the optimal duration of intubation attempts.

Methods: Observational study at The Royal Women's Hospital, Melbourne. A secondary analysis was performed of video recordings of neonates ≤ 32 weeks' postmenstrual age undergoing elective intubation. Infants received premedication including atropine, a sedative and muscle relaxant. AOT was defined as the time between the last positive pressure or spontaneous breath and a decrease in SpO2 to below 90%.

Results: Seventy-eight infants were included. The most common reasons for intubation were respiratory failure (58/78 [74%] infants) and apnoea (13/78 [17%]). All but five infants (6%) desaturated to SpO2 <90% during the apnoeic period. The mean (SD) AOT (time to SpO2 <90%) was 25.3 (19.4) seconds. The mean (SD) time to SpO2 <80% (58/78 infants) was 37.0 (21.9) seconds, and to SpO2 <60% (31/78 infants), 58.2 (20.2) seconds. No bradycardia (HR <100 beats per minute) was observed in any infant. There was no correlation between AOT and GA (r=-0.04, p=0.71), birth weight (r=-0.19, p=0.11) or age at intubation (r=0.15, p=0.20). There was a weak correlation between lower supplemental oxygen administration prior to intubation and a longer AOT (r=-0.25, p=0.03).

Conclusions: This is the first study to report AOT in preterm infants. AOT is substantially shorter in preterm infants compared with pediatric and adult patients and there is only a short time in which to safely perform endotracheal intubation. These data provide important clinical information for the development of clinical guidelines and studies to improve neonatal intubation safety.

PAEDIATRICS

Duodenal Atresia associated with limb and craniofacial anomalies in human subjects: a case for the role of FGF10?

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Duodenal atresia (DA) is a congenital bowel aberration affecting 1/7000 pregnancies and categorised into 3 types according to severity of luminal obstruction. Approximately 20 Victorian families in our community, each year, are impacted by their newborn's diagnosis of DA. The cause of DA is unknown, however associations with genetic anomalies supports a genetic aetiology. Taken together, this highlights the very real importance and therapeutic relevance of understanding the cause of duodenal atresia. In humans, DA is associated with Down Syndrome in 20-30% cases. In mice, FGF10-FGFR2b pathway interruption is associated with DA in 35-74% homozygous knockouts. It has been well-described that FGF10 null knockout mice universally lack limbs and have abnormal craniofacial features. Importantly, in humans FGF10-FGFR2b interruption is associated with craniofacial and limb abnormalities, e.g. Lacrimo-auriculo-dento-digital syndrome.

We hypothesise that DA patients with craniofacial or limb anomalies represent a cohort likely to demonstrate FGF10-FGFR2b pathway mutations. To better understand this cohort, we queried an ethics-approved database of 135 DA cases for DA patients with craniofacial or limb anomalies. Cases were retrospectively reviewed for DA type, anomaly phenotype, and genetic assessments. Genetic comparison analysis was performed between murine RNA genes extracted from duodenal tissue and selected craniofacial and limb human genes.

13/135 (10%) DA cases were identified to have craniofacial and/or limb anomalies. A 14th eligible patient was excluded due to early death limiting available information. 6/13 were type 1 DA, and 7/13 type 3. 10/13 had a diagnosed syndrome: 2/13 Down, 2/13 CHARGE, 3/13, VACTERL, 2/13 Feingold and 1/13 Goldenhar. 5/13 had only craniofacial anomalies, 5/13 craniofacial and/or limb anomalies, and 3/13 only limb anomalies. Early observations show upper limb preaxial abnormalities and hearing loss as the predominant limb and craniofacial anomalies. A total of 44 genes were identified as potential candidate genes for DA.

Identification of FGF10-FGFR2b pathway anomalies in human DA patients would advance understanding of DA aetiology, as well as normal duodenal morphogenesis. This would immediately open the door to superior genetic and antenatal counselling, as well as potential future therapies for patients with duodenal atresia and their families. We plan detailed genetic phenotyping and exon sequencing of this DA cohort, supported by parallel murine model studies to confirm the role and requirement of candidate mutations for duodenal atresia generation.

PAEDIATRICS

Post-operative Colonic Manometry in Children with Hirschsprung Disease: A Systematic Review

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Introduction: A significant proportion of children experience bowel dysfunction, including constipation and faecal incontinence, following surgical repair of Hirschsprung disease (HD). Persistent symptoms are thought to relate to underlying colonic and/or anorectal dysmotility. Manometry may be used to investigate the gastrointestinal motility patterns of this population. We sought to: (1) Evaluate the colonic manometry equipment and protocols used in the assessment of the post-operative HD population. (2) Summarise the available evidence regarding colonic motility patterns in children with HD following surgical repair.

Methods: We performed a systematic review of the Cochrane Library, Embase, MEDLINE, and PubMed databases (1st January 1980 and 9th March 2020). Data were extracted independently by two authors. This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies reporting the postoperative assessment of children with HD using colonic manometry were considered for inclusion.

Results: Five studies satisfied selection criteria, providing a combined total of 496 children. Of these, 184 children with repaired HD underwent colonic manometry. Studies assessed heterogeneous populations, utilised variable manometry equipment and protocols, and reported limited baseline symptom characteristics, thus restricting comparability. All studies used low-resolution colonic manometry.

Conclusion: This systematic review highlighted the paucity of evidence informing the understanding of colonic dysmotility in the post-operative HD cohort. Current literature is limited by variable methodology and heterogeneous cohorts, restricting the comparable outcome data available. No studies were identified that utilised high-resolution manometry.

PAEDIATRICS

Functional characterisation of neurodevelopmental disorder-associated mutations in synaptotagmin-1

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Introduction: Next generation sequencing is allowing the genetic diagnosis and mechanistic understanding of a range of neurodevelopmental disorders associated with presynaptic neurotransmitter release machinery. This is not only improving patient management, but also informing the function of affected proteins and amino acids. Accordingly, we have recently identified the first known cases of human mutations in synaptotagmin-1 (SYT1), an essential synaptic vesicle protein that acts as the calcium-sensor triggering fast, synchronous neurotransmitter release, which has auxiliary roles in other aspects of synaptic physiology. Five de novo missense variants were found in individuals exhibiting a phenotypic spectrum of common symptoms including motor delay, intellectual disability, movement disorders and behavioural abnormalities. We aimed to interrogate the impacts of these mutations on SYT1 function and the dynamics of neurotransmitter release.

Methods: Live cell imaging of a pHluorin reporter, a pH-sensitive fluorescent protein, was used to assay synaptic vesicle fusion and recycling. Rat SYT1 tagged with pHluorin and harbouring patient mutations was expressed in cultured wild-type mouse hippocampal neurons. pHluorin fluorescence was monitored in response to multiple electrical stimulation paradigms and immunocytochemistry was performed to determine mutant SYT1 expression levels and subcellular localisation.

Results : All but one SYT1 variant localised correctly to synaptic vesicles ($p<0.05$, n=3-8) and expressed similarly to the wild-type protein ($p<0.01$, n=3-4). pHluorin live imaging revealed that SYT1 mutants differentially slow the rate of evoked exocytosis in a dominant-negative manner ($p<0.05$, n=5-7), and notably this slowing was less pronounced for the variant presenting with a less severe clinical profile. Spontaneous neurotransmitter release and synaptic vesicle endocytosis were unaffected in the presence of any SYT1 mutants. Importantly, exocytic efficiency could be rescued by increasing extracellular calcium concentration ($p<0.05$, n=7-8).

Conclusion: These findings demonstrate that mutation-specific impairment of calcium-dependent neurotransmitter release is the major pathophysiological mechanism underpinning this novel disorder. Furthermore, we provide proof of principle that neurotransmission can be normalised, thereby suggesting potential therapeutic avenues for this syndrome.

PAEDIATRICS

Diagnosis and functional characterisation of the mitochondrial disease-associated ATAD3 gene cluster

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Mitochondrial disease encompasses a heterogeneous group of disorders caused by mutations in ~350 known mitochondrial genes, affecting ~1:5000 births. The substantial clinical, biochemical and genetic heterogeneity of mitochondrial disorders poses an immense challenge for molecular diagnosis, with many cases remaining unsolved. The ATAD3 locus is a cluster of three highly homologous, tandemly arrayed nuclear-encoded mitochondrial genes (ATAD3A, ATAD3B, and ATAD3C). Previously refractive to study due to the highly repetitive nature of the genomic region, the ATAD3 locus has emerged as one of the five most common causes of paediatric cases of nuclear-encoded mitochondrial disease. The high degree of homology also renders the genomic region susceptible to a range of pathogenic copy number variations, including intergenic deletions and duplications. We have developed a quantitative proteomics based approach, that when combined with other genomic data allowed us to identify de novo ATAD3 duplications in a cohort of 17 subjects from 16 unrelated families with cardiomyopathy, persistent hyperlactacidemia, and frequently corneal clouding or cataracts (Frazier et al. 2020 Med1). The duplications all resulted in the formation of an identical chimeric ATAD3A/ATAD3C protein, confirmed by quantitative proteomics, which appears to act in a dominant manner causing altered ATAD3 complexes and a striking reduction in mitochondrial OXPHOS complex I activity in heart tissue. Similarly, patients harboring deletions in the ATAD3 cluster presented with decreased abundance of peptides that match the deleted genetic region in the protein. We are now applying the proteomics techniques we have developed here and elsewhere, along with gene-edited cell lines and patient derived iPSC lineages to functionalize the genes encoded by the ATAD3 locus. By further developing these quantitative techniques and elucidating the functional role of the ATAD3 genes, we aim to improve the diagnostic efficiency and yield of mitochondrial disease cases caused by this prevalent gene cluster.

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