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De novo PIK3CB mutation associated with macrocephaly and diffuse polymicrogyria

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Background: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta (PIK3CB) is a member of the PI3K complex. This complex has two p110 members; PIK3CA (p110a) and PIK3CB (p110b) which are both ubiquitously expressed. PI3K complex functions to phosphorylate PIP2 to PIP3 which activates AKT and subsequently mTOR. PIK3CA mutations have been previously linked with macrocephaly and developmental delay. **Methods:** An 18 month old girl was investigated for severe hypotonia, developmental delay and macrocephaly. Head circumference was >97%ile at birth and 53.0 cm (>99%ile, +5.4 SD) at 13 months old. She had no hydrocephalus or epilepsy. MRI brain (18 months old) re-identified megalencephaly and diffuse polymicrogyria. Symmetric signal abnormality was noted in the periventricular white matter, unchanged between 8 and 18 month images. MR spectroscopy was unrevealing. At 18 months she remains unable to sit independently. Exome sequencing was performed and functional studies to further support variant pathogenicity. **Results:** Exome sequencing identified de novo variant in PIK3CB: c.1735G>T; p.Asp579Tyr. No mutations were noted in other genes known to cause developmental delay, macrocephaly or overgrowth syndromes. Functional studies in patient cells showed dysregulation of PIK3CB and downstream signalling, providing support for causality of this novel disease gene. **Conclusions:** We believe that our patient's macrocephaly (+5.4 SD) and diffuse polymicrogyria results from altered PIK3CB function.

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Redesign of a neuropsychology service in a tertiary pediatric hospital (CHEO)

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Background: Neuropsychological assessments are used in hospitals to examine brain-behaviour relationships, and are an integral part of care for medically complex patients. Unfortunately, waitlists can be lengthy. We gathered information regarding best-practice guidelines and physician referral patterns in an effort to better manage the neuropsychology waitlist at a pediatric hospital. **Methods:** We conducted: 1) A semi-structured telephone survey with 4 Canadian, pediatric, hospital-based neuropsychology services; 2) An electronic survey distributed to referring physicians at CHEO; 3) A focus group for CHEO neurologists and neurosurgeons. **Results:** The telephone survey indicated that there are no clear, best-practice guidelines for pediatric neuropsychologists working in a tertiary, pediatric hospital. The electronic survey revealed some confusion about neuropsychology services and indicated the need for better communication between neuropsychology and referral sources. The focus group revealed that demand for neuropsychology services far outstrips supply and confirmed the need for better communication. **Conclusions:** The results confirmed the need for best-practice guidelines to be developed around delivering neuropsychology services within a pediatric tertiary care setting, as well as continuing to work closely with neurology and neurosurgery to ensure that the neuropsychological needs of their patients are met.

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Expanding the phenotype of TRNT1 mutations to include Leigh syndrome

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Background: Children with biallelic mutations in *TRNT1* have multi-organ involvement with congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay (SIFD) as well as seizures, ataxia and sensorineural hearing loss. The *TRNT1* gene encodes the CCA-adding enzyme essential for maturation of both nuclear and mitochondrial transfer RNAs accounting for phenotypic pleitropy. Neurodegenerative Leigh syndrome has not been previously reported. **Methods:** Case summary: A Portuguese boy presented with global developmental delay, 2 episodes of infantile Leigh encephalopathy at 8 mo and 4 yr responsive to high-dose steroids, slow neurodegeneration of cognitive, language and motor functions with optic atrophy, pigmentary retinopathy, spasticity, dystonia, and focal dyscognitive seizures, pancytopenia, transfusion dependent sideroblastic anemia, recurrent febrile infections (pulmonary, gastrointestinal), hypernatremia, with tracheostomy dependence at age 5 yr, malabsorption and TPN dependence at 9 yr, and survival to early adulthood. Neuroimaging showed symmetric hemorrhagic lesions in the thalamus, brain stem (periaqueductal grey) and cerebellum consistent with Leigh syndrome but no lactate peak on MRS. **Results:** Whole exome sequencing identified a homozygous missense pathogenic variant in *TRNT1*, c.668T>C (p.I223T) in the affected individual. **Conclusions:** This report expands the neurological phenotype of *TRNT1* mutations and highlights the importance of considering this gene in the evaluation of Leigh syndrome.

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Infantile Onset Multisystem Neurologic, Endocrine and Pancreatic Disease: case series and review

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Background: We report three brothers born to consanguineous parents of Syrian descent with a novel homozygous c.324G>A (p.W108*) mutation in PTRH2 that encodes mitochondrial peptidyl-tRNA hydrolase 2. Mutations in PTRH2 have recently been identified in the autosomal recessive condition, Infantile Onset Multisystem Neurologic, Endocrine and Pancreatic Disease (IMNEPD). To our knowledge, this is the first case of IMNEPD described in a Canadian centre. **Methods:** Clinical phenotyping enabled a targeted approach in which all exons of PTRH2 were sequenced. We identified a novel mutation and compared our patients with those recently described. **Results:** We identified a homozygous nonsense mutation in PTRH2, c.324G>A (p.W108*). This G to A mutation results in a premature stop at codon 108 that produces a truncated protein, removing most of the amino acids at the enzymatic active site. This mutation is not

listed in the human Gene Mutation Database Cardiff, NCBI dbSNP, 1000 Genomes, Exome Variant Server or ClinVar and is a rare variant listed in gnomAD. **Conclusions:** In IMNEPD, nonsense mutations in PTRH2 appear to cause severe disease with postnatal microcephaly, neurodevelopmental regression, and ataxia with additional features of seizures, peripheral neuropathy, and pancreatic dysfunction, whereas missense mutations may produce a milder phenotype. The spectrum exhibited by our patients suggests variable expressivity with PTRH2 mutations.

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Autism-associated mutations in SHANK2 increase synaptic connectivity and dendrite complexity in human neurons

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Background: Heterozygous loss-of-function mutations in the synaptic scaffolding gene *SHANK2* are strongly associated with autism spectrum disorder (ASD). However, their impact on the function of human neurons is unknown. Derivation of induced pluripotent stem cells (iPSC) from affected individuals permits generation of live neurons to answer this question. **Methods:** We generated iPSCs by reprogramming dermal fibroblasts of neurotypic and ASD-affected donors. To isolate the effect of *SHANK2*, we used CRISPR/Cas9 to knock out *SHANK2* in control iPSCs and correct a heterozygous nonsense mutation in ASD-affected donor iPSCs. We then derived cortical neurons from SOX1+ neural precursor cells differentiated from these iPSCs. Using a novel assay that overcomes line-to-line variability, we compared neuronal morphology, total synapse number, and electrophysiological properties between SHANK2 mutants and controls. **Results:** Relative to controls, *SHANK2* mutant neurons have increased dendrite complexity, dendrite length, total synapse number (1.5-2-fold), and spontaneous excitatory postsynaptic current (sEPSC) frequency (3-7.6-fold). **Conclusions:** ASD-associated heterozygous loss-of-function mutations in *SHANK2* increase synaptic connectivity among human neurons by increasing synapse number and sEPSC frequency. This is partially supported by increased dendrite length and complexity, providing evidence that SHANK2 functions as a suppressor of dendrite branching during neurodevelopment.

Spine and Peripheral Nerve surgery

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Quantifying potential sources of delay in surgical management of cervical spondylotic myelopathy

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Background: Cervical spondylotic myelopathy is a degenerative condition with a variable clinical course. We aim to quantify the sources of potential delay in management and understand how the timing of these events may affect quality of life measures. **Methods:** The Canadian Spine Outcomes Research Network Registry was used to identify patients older than 18 years of age and have received cervical decompression surgery from January 1, 2013 to March 1, 2016. The primary outcome was the Short Form-12 Physical Component Score at 12-month follow-up. Four time groups were identified: 1) duration of symptoms, 2) time awaiting surgical consult, 3) time spent monitoring symptoms, and 4) time awaiting surgery. Multivariate regression was used for analysis. **Results:** A total of 208 patients were identified. The mean age was 59.5 years. 61.53% of patients had symptoms for >12 months at initial consult. Mean time awaiting surgical consult, monitoring symptoms, and awaiting surgery was 77.2, 60.9, and 46.9 days, respectively. Time awaiting surgery (β=-0.032, p=0.04) was a significant factor for change in Physical Component Score. **Conclusions:** We found time awaiting surgery to be a significant factor on PSC score at 12-month follow-up. Increased time awaiting surgery may result in negative impacts on quality of life outcomes.

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Use of intravenous fluorescein for intra-operative localization of an intramedullary spinal cord tumour; a technical note

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Background: Localization of intramedullary spine tumors can be difficult. Various intraoperative aids have previously been described, but have limited use due to expense, complexity, and time. Intravenous fluorescein is an inexpensive and safe drug that may be useful in the localization of such tumors. We describe a technical description of the intra-operative use of fluorescein as an aid in the localization of a intramedullary spine tumour. **Methods:** In this technical report, the authors present a case example of a 56 year old man presenting with a intramedullary tumor at the level of C5/6. Intraoperatively intravenous Fluorescein was administered and the Pentero microscope BLUE™ 400 feature was used to accurately identify the lesion. Multiple biopsies of the fluorescent tissue were taken. **Results:** After 10 cardiac cycles the fluorescent coloring was isolated to what was thought to be the intramedullary lesion. Our myelotomy was made based on the uptake of this fluorescent coloring and multiple biopsies were taken. Final pathology confirmed this tissue was consistent with a high grade glioma. **Conclusions:** The use of intravenous fluorescein was a valuable aid in localizing the lesion and minimizing the size of our myelotomy. The use of intravenous